Catalytic electronic activation: The addition of nucleophiles to an allylic alcohol

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Catalytic Electronic Activation: The Addition of Nucleophiles to an Allylic Alcohol

submitted by Phillip James Black

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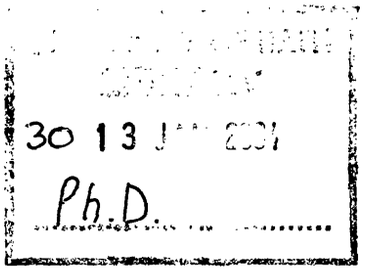
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The work described in this Thesis is entirely my own, except where I have acknowledged either help from a named person or a reference is given to a published source or Thesis. Text taken from another source will be enclosed in quotation marks and a reference will be given.

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Abstract

This report describes a number of methods to activate 2-cyclohexen-1-ol **112** and 2-cyclopenten-1-ol **173** through the use of aluminium-catalysed transfer hydrogentation. The electronically activated substrates are demonstrated to undergo facile conjugate addition and, when the alcohol functional group is subsequently restored in a *one-pot* procedure this leads to an indirect addition of nucleophiles to allylic alcohols. This novel methodology has been termed **Catalytic Electronic Activation** (CEA).

The aluminium *tert*-butoxide catalysed conversion of 2-cyclohexen-1-ol **112** into 2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile **168** and 2-cyclopenten-1-ol **173** into 2-(3-Hydroxy-cyclopentyl)-2-methyl-malononitrile **175** in 90% and 60% yield respectively has been demonstrated through an efficient domino Oppenauer/Michael addition/MPV process.

Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Ar	Unspecified aryl group
ax	Axial
BINOL	1,1'-Bi-2-napthol
Bn	Benzyl
BnBr	Benzyl bromide
b.p.	Boiling point
Bu	Butyl
CEA	Catalytic Electronic Activation
COD	1,5-Cyclooctadiene
Da	Daltons
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
DIBAL	Diisobutylaluminium hydride
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPAT	Diphenylammonium triflate
EDBP	2,2-ethylidenebis(4,6-di-*tert*-butylphenol)
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EI	Electron Impact
eq	Equatorial
Et	Ethyl
h	Hour
HPLC	High Performance Liquid Chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz

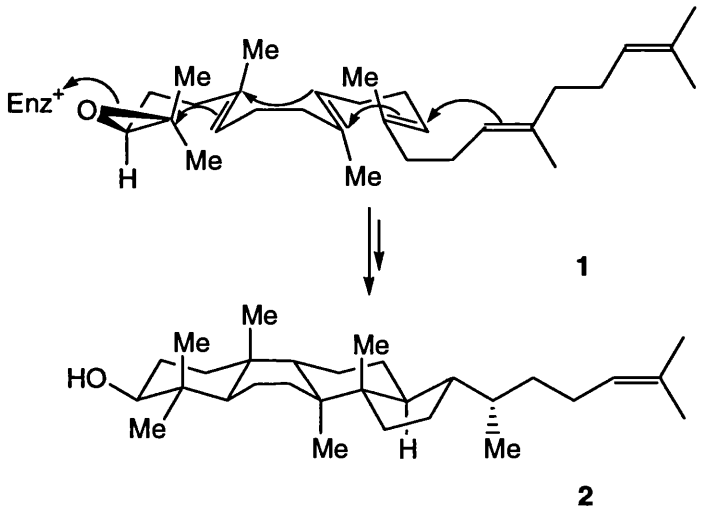
i	*iso*
*i*PA	isopropanol
*i*Pr	*iso*-Propyl
FT-IR	Fourier Transform Infra-red
J	Coupling constant
LHMDS	Lithium hexamethyldisilazide
M	Molar
Me	Methyl
MeOH	Methanol
MeCN	Acetonitrile
MMPEP	2,2'-methylenebis(4,6-di(1-methyl-1-phenylethyl)phenol
MPV	Meerwein-Ponndorf-Verley
MPVO	Meerwein-Ponndorf-Verley-Oppenauer
MS	Mass Spectrometry
n	*normal*
N	Moles per litre
NMR	Nuclear Magnetic Resonance
Nuc	Unspecified nucleophile
p	*para*
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
Py	Pyridine
R	Unspecified alkyl group
RT	Room temperature
s	*sec*
SET	Single Electron Transfer
t	*tert*
*t*Bu	*tert*-butyl
TBAB	Tri-butylammonium bromide
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	tri-Methylsilychloride
TPP	5,10,15,20-tetraphenylporphinato

Chapter 1

1.1 Sequential Reactions

In the early days of organic synthesis only simple molecules were prepared. In the meantime, the complexity of target molecules has increased considerably. The current pinnacle has been reached with the synthesis of palytoxin with sixty four-stereogenic centres,[1] of which, in principal, over 10^{19} stereogenic forms can exist. For this reason it has been necessary to develop chemical transformations with increasingly higher selectivity. Thus, in the past few years a wealth of chemo-, regio-, diastereo-, and enantioselective reactions have been discovered and developed, the selectivity of which frequently approaches that of enzymatic processes. Nevertheless, if we compare our synthetic performance to date with that of Nature, then we must recognise that Nature is not just highly selective, but also very efficient, often employing sequential transformations. By this we understand a series of reaction steps in which several bonds are formed or broken, without the isolation of any intermediates.

A particularly fascinating example from Nature is the cyclisation of squalene oxide **1** (Scheme 1) to give lanosterol **2**, a starting material for many steroids.[2]



Scheme 1 Cyclisation of squalene oxide

Sequential reactions are characterised by their great elegance, frequently high stereoselectivity and by the simple manner in which they may be carried out. Moreover, the development of this type of synthetic method can lead to a reduction in the amount of undesired by-products, thereby contributing to the protection of the environment. For example, the quantity of solvents and eluents required in

comparison with stepwise processes is considerably reduced; one of the main problems in the chemical industry is the treatment of chemical waste and the search for environmentally tolerable procedures for chemical production. Sequential reactions might, therefore, be more frequently included in future synthetic planning.

Sequential transformations, which are known to chemists under the all-embracing term *one-pot* reactions, have been reviewed extensively by Tietze[3-7] and Waldmann.[8] In these reviews two classes of sequential transformations are defined:

- Domino Reactions[9-12]

- Consecutive Reactions[13-16]

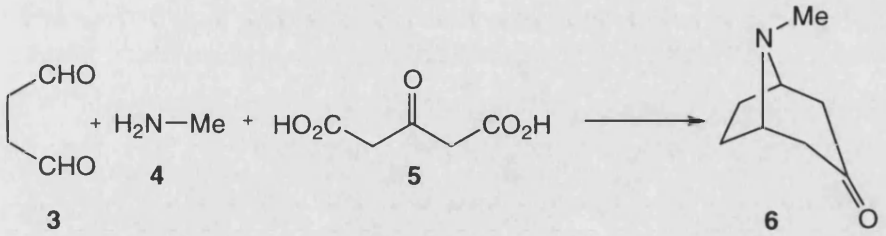
A *domino reaction*, frequently also described as *tandem* or *cascade reaction*, is defined as "a process involving two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step." This suggests that a *steady-state* concentration of the intermediate is formed.

In a *consecutive* reaction, "another reagent, mediator, or catalyst is added *after* the first transformation without isolation of the first formed product; the subsequent reaction steps then lead to the final product.

Domino reactions are further classified by taking as a basis the reaction type of the first two steps. According to the mechanism of the first step, one can distinguish between a cationic, anionic, radical, pericyclic, photochemical, and transition-metal induced transformation which can be combined with reactions of the described type in a second, a third, or even a fourth step. Combinations of reactions of the same mechanism are called homo-domino reactions, whereas sequences of reactions with different mechanisms are called hetero-domino reactions. There is not the space to adequately describe all the known domino reactions, however the scope of the domino reaction is exemplified by the diverse examples illustrated in Schemes 2, 3 and 4.

Domino reactions have been utilised from early on in the history of organic synthesis. One of the first laboratory examples was Robinson's elegant synthesis of tropinone **6**

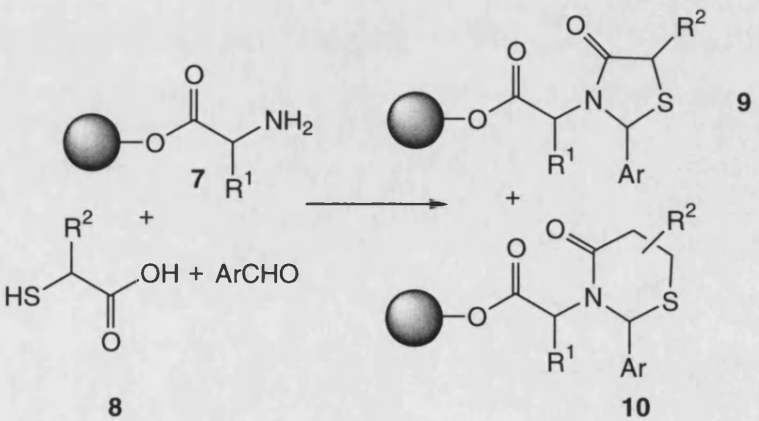
by mixing succindialdehyde **3**, methylamine **4** and acetonedicarboxylic acid **5**[17] (Scheme 2).



Scheme 2 The biomimetic domino synthesis of tropinone

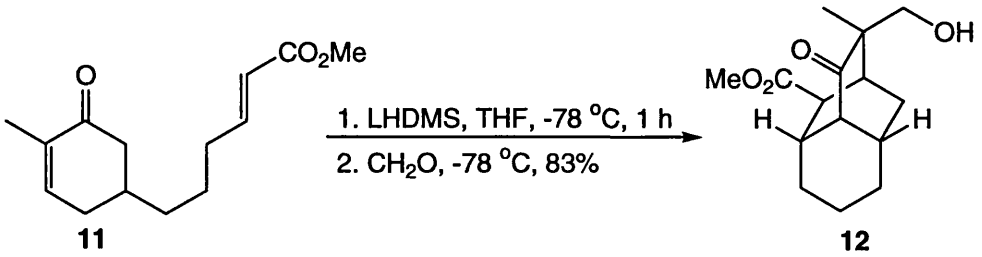
Many chemists have since recognised the potential of domino reactions and they have subsequently featured in the most recent of synthetic methodologies: combinatorial chemistry. The synthesis of important organic molecules for use as drugs, diagnostics, agrochemicals, dyes and materials is one of the main bases of the chemical industry. For the design of these substances, novel, and highly efficient syntheses must be developed that not only allow the preparation of small-molecule libraries in a combinatorial fashion, but also give access to a high structural diversity. Thus, examples of domino reactions on solid supports for the preparation of libraries have been widely reported in the literature.[6]

For example, sulfur-containing heterocycles have been generated on a solid-support in a multicomponent reaction as illustrated by Holmes and co-workers.[18] The condensation of a polymer-bound amino acid **7**, an α-mercapto carboxylic acid **8** and an aldehyde leads to the formation of thiazolidinones **9** and metathiazanones **10** respectively (Scheme 3).



Scheme 3 Synthesis of thiazolidinones and metathiazanones

The anionic homo-domino reaction is the most often encountered domino reaction in the literature, especially for systems combining two Michael additions. Thus, the skeleton of natural products such as seychellene and patchouli alcohol can easily be obtained by employing this type of reaction.[19] Thus, reaction of **11** with the strong base LHDMS followed by treatment with gaseous formaldehyde afforded the tricyclo[5.3.1.0]undecane **12** in 83% yield as a single isomer (Scheme 4).



11 **12**

Scheme 4 Anionic homo-domino reaction

These three syntheses provide only a brief highlight from the wealth of applications of domino reactions, however the potential of this synthetic approach and possible future developments are enormous.

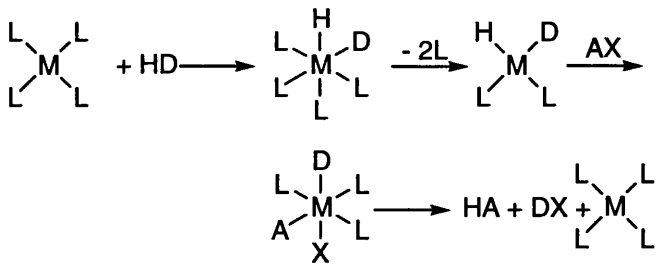
1.2 Oxidation and Reduction Reactions

The oxidation and reduction of organic compounds is synthetically important both in the academic laboratory and within industry. Many metals in the transition period have variable oxidation states and these properties have made them very useful for the oxidation and reduction of many compounds.[20,21] Ever since the independent discovery of the Meerwein-Ponndorf-Verley (MPV) reaction by Meerwein,[22] Ponndorf[23] and Verley[24] in which a ketone is reduced by an alcohol in the presence of an aluminium alkoxide, the use of metallic compounds (both hetero- and homogeneous) to promote hydrogen transfer between alcohols and carbonyl compounds has been widely studied in organic synthesis. In 1952, both Braude and Linstead[25,26] made the pioneering suggestion that heterogeneous catalytic hydrogen transfer from an organic donor molecule to a variety of organic acceptors might be possible under mild conditions. This is a distinctly different process to catalytic reduction using molecular hydrogen (or hydride) as the source of hydrogen (Scheme 5)[27,28] thus avoiding the associated hazards and expense.

A) Hydrogen-atom-transfer reaction:

$$A^{\cdot} + HD \longrightarrow AH + D^{\cdot} \longrightarrow \text{etc}$$

B) Homogeneous transfer hydrogenation:



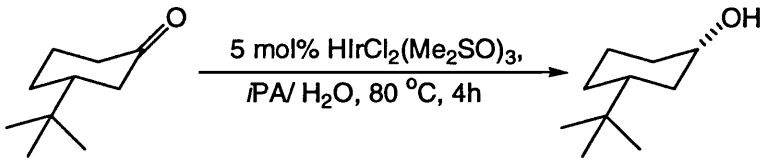
HD = hydrogen donor molecule
A = reducible organic acceptor substrate

Scheme 5 Comparison of hydrogen transfer mechanisms

More recently, transition metal-catalysed versions of these reactions have been developed and the subject reviewed extensively.[29-33] Today, the asymmetric transfer hydrogenation[34-36] of prochiral ketones is one of the most attractive methods for synthesising enantiomerically enriched secondary alcohols, which form an important class of intermediates for fine chemicals and pharmaceuticals.

Transfer hydrogenation is defined as "*the reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst*".[31] In this respect, formic acid and formates, phosphinic acid and phosphinates, hydrazine, hydrides of boron, aluminium, silicon, and tin, alcohols, amines, and hydrocarbons can all act as hydrogen donors in catalytic reduction. An added advantage is gained when the products of the decomposing donor have large negative enthalpies of formation. Thus CO_2 from formic acid and N_2 from hydrazine provide added driving force to the reactivity of these substances as hydrogen donors; the formation of gaseous products is also an entropically favourable process. The list of hydrogen acceptors includes ketones, α,β-unsaturated carbonyl compounds, α,β-unsaturated acids and esters, imines and nitro compounds.

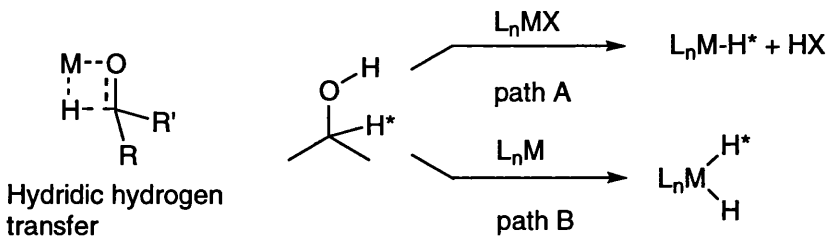
The majority of the elements that have proved valuable in forming compounds suitable for catalytic homogeneous hydrogenations form part of the second transition series in the periodic table. Although the first reported example of a homogeneous transition metal-catalysed hydrogen transfer used an iridium hydride-DMSO complex (Scheme 6)[37], the most active catalysts are to be found in the salts and complexes of Rh[34], Ru[38] and Pd[39] which can be used at very low loadings, typically less than 1 mol% catalyst.



13 **14**

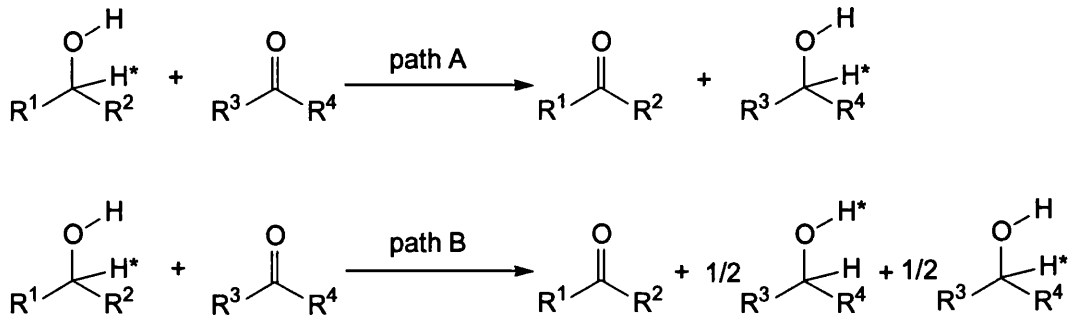
Scheme 6 Reduction of 3-*tert*-butylcyclohexanone with $HIrCl_2(Me_2SO)_3$

The mechanism of transition metal catalysed hydrogen transfer has recently been re-evaluated by Bäckvall[32] who has distinguished two different possible pathways for the metal-hydride *hydridic* mechanism (Scheme 7).



Scheme 7 Pathways proposed for hydridic transfer hydrogenation

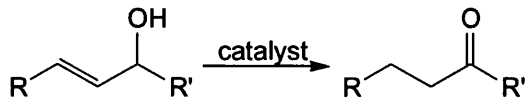
Thus, the metal hydride may arise purely from the C-H of the alcohol (Scheme 7, path A) or it may originate from *both* the O-H and the C-H (Scheme 7, path B). Therefore, for path B *either* of the hydrides on the metal may add to the carbonyl carbon and it is prudent to ask whether the hydrogen atoms transferred maintain their identity, i.e. if O-H is transferred to keto oxygen and C-H to carbonyl carbon (Scheme 8, path A) or if the two hydrogens are scrambled and their identity lost (Scheme 8, path B).



Scheme 8 Possible paths for direct hydrogen transfer

Racemisation studies on an enantiomerically pure deuterium-labelled alcohol using rhodium, iridium and ruthenium complexes with various phosphorus, nitrogen and sulfur ligands as transfer hydrogenation catalysts did indeed confirm that there are two competing pathways. Whilst rhodium and iridium appear to follow the metal monohydride mechanism (Scheme 7, path A), ruthenium adopts both the metal dihydride and monohydride mechanisms (path B and A respectively)[32]

However, with reference to the current study, the ability of transition metals to catalyse isomerisation of allylic alcohols to saturated ketones must be considered[40,41] (Scheme 9).



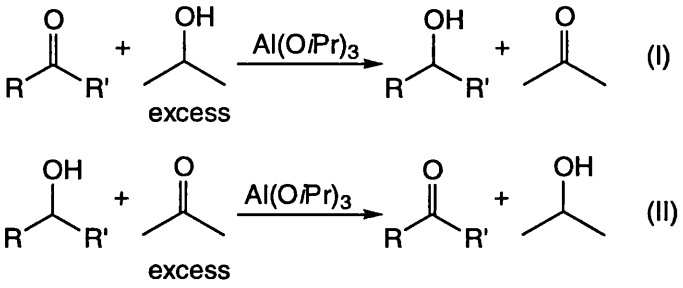
Scheme 9 Isomerisation of allylic alcohols to saturated ketones

Depending on the metal catalyst employed, the reaction can occur *via* different mechanisms and although metal-catalysed double bond migration to form an enol is the most common pathway,[42] it is likely that a ruthenium-catalysed isomerisation involves intramolecular hydrogen transfer *via* dehydrogenation of the alcohol and subsequent transfer of the hydrogens (hydrides) to the double bond.[40]

It is for this reason that aluminium (Meerwein-Ponndorf-Verley type) catalysts were chosen for their ability to effect transfer hydrogenation (Appendix 1).

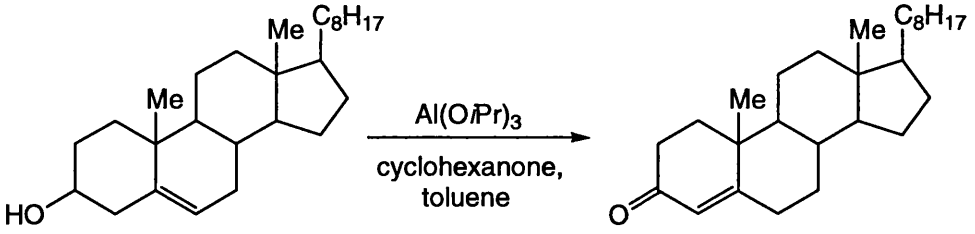
1.3 The Oppenauer oxidation and Meerwein-Ponndorf-Verley reduction

Hydrogen transfer reactions in which 1 mole of hydrogen is transferred from an alcohol to a ketone have been known since 1925 when Meerwein and Schmidt[22] performed the reduction of chloral (trichloroethanal) with ethanol in the presence of aluminium ethoxide. Independently, Verley[24] and then Ponndorf[23] extended the scope of the reaction to the reduction of aldehydes and ketones by means of an easily oxidisable secondary alcohol. In the original version aluminium isopropoxide was used to promote transfer of hydrogen from isopropanol to a ketone and this reduction is now referred to as the Meerwein-Ponndorf-Verley (MPV) reduction after its discoverers (Scheme 10, equation I).



Scheme 10 Meerwein-Ponndorf-Verley reduction and Oppenauer oxidation

The reaction can also be run in the opposite direction (Scheme 10, equation II) and this was subsequently studied by Oppenauer[43] during his work on sterol ketones and sex hormones in the 1930s. This oxidation appeared to be superior to contemporary oxidation methods because of its high yield, chemoselectivity and mild reaction conditions, especially in the synthesis of natural products and analogues (Scheme 11).



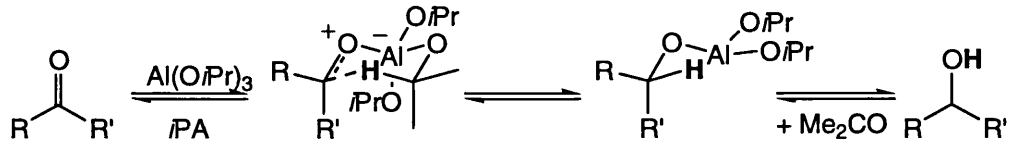
15 **16** 72-74%

Scheme 11 Oxidation of cholesterol 15 to cholestenone 16[44]

The literature on MPV and Oppenauer reactions until 1950 is covered by comprehensive reviews by Wilds[45] and Djerassi[46] and more recently by de Graauw.[47]

The length of time between the earlier and most recent reviews indicates the synthetic dominance of complex metal hydrides, such as $LiAlH_4$ and catalytic hydrogenation over heterogeneous metal catalysts in the intervening years. However, the MPVO reactions have many practical advantages: for example, chemoselectivity under mild reaction conditions, regioselectivity and ease of adaptability for both laboratory and large-scale synthesis.

In contrast to the mechanism of hydride transfer for transition metals it is generally accepted (after much mechanistic conjecture in the late 1940s and early 1950s)[48-56] that MPVO reactions proceed *via* a cyclic complex in which both the carbonyl compound and the reducing alcohol are bound to the metal ion: direct hydrogen transfer (Scheme 12).[57,58] Subsequent hydride transfer, separation from the complex of the ketone produced and rate-determining alcoholysis of the mixed alkoxide, liberating the free alcohol, thus completes the cycle.



Scheme 12 Mechanism of the MPVO reaction

In support of this mechanism deuterium tracer studies indicate that the hydrogen transferred to the carbonyl does come from the carbinol (alcohol) carbon.[59,60] Pickart and Hancock[48] found a Hammett ρ-constant of 1.296 for the equilibrium between substituted benzophenone and diethylcarbinol. Thus, increased positive character of the carbonyl group facilitates the reaction, which is compelling evidence for hydride transfer. In fact, Shiner *et al.*[51] have proved that the hydride transfer step of the MPV reaction must involve a polymeric form of aluminium alkoxide.

However, by 1960 Moulton *et al.*[49] had begun to question the validity of this mechanism. Through careful kinetic studies they discovered that satisfactory rate constants were only obtained when the catalyst concentration was raised to the 1.5 power. Therefore, they proposed that the reaction proceeds by two different mechanisms: one of these is the accepted mechanism; the other must involve two molecules of catalyst to fit the kinetic data. A process in which the hydride ion is transferred to the carbonyl carbon from a molecule of aluminium isopropoxide other than the one coordinated through aluminium to the carbonyl oxygen would meet this

condition (Figure 1). However, a later study by Shiner *et al.* [50] has suggested that the anomalous rate data could be explained by the differing reactivities of the slowly interconverting polymeric forms of aluminium alkoxide.

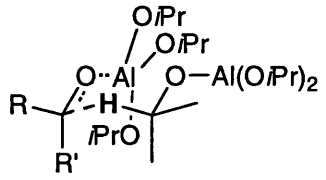


Figure 1 Proposed structure of trimolecular MPVO transition state

Although von Doering *et al.*[59] reported that a free-radical mechanism was unlikely to be involved in the MPVO reaction, recent work on Single-Electron-Transfer (SET) by Ashby *et al.*[61,62] has proposed that it is possible to envision the reaction taking place *via* a radical transition state (Figure 2).

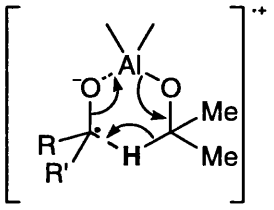


Figure 2 Proposed MPVO radical transition state

However, this mechanism does appear to be confined to the MPVO reaction using alkali metal alkoxides rather than aluminium reagents i.e. aluminium isopropoxide is an inferior one-electron donor than lithium alkoxide. Nevertheless, Bäckvall's recent study on the mechanism of metal-catalysed hydrogen transfer[32] discovered that for both aluminium and samarium a partial involvement of another mechanism in addition to the direct hydrogen transfer route was evident: this may be accounted for by an electron transfer pathway (*vide supra*).

These hydrogen transfer reactions are equilibrium reactions, which can be forced in either direction by the use of an excess of either alcohol or ketone in the starting materials. Thus, for the MPV reduction of a ketone, isopropanol is employed in excess, often as the reaction solvent. Of the alcohols, secondary ones have proved to be the best hydrogen donors and it is the hydrogen on the carbon attached to the hydroxyl (α-hydrogen), which is transferred in the first reductive step. Tertiary alcohols having no α-hydrogen atoms are not hydrogen donors and under the influence of catalysts, tend to condense to form ethers or to eliminate water to form

alkenes.[63] Despite the variety of alcohols used, isopropanol remains the most popular donor, because of its simplicity, cheapness, availability and the ease of removal of both it and its dehydrogenation product, acetone, from reaction systems.

An insight into the thermodynamics of the MPVO equilibria provides a theoretical basis for the suitability of solvents such as isopropanol as hydrogen donors. Adkins *et al.* [64] have determined by polarography relative reduction potentials for a wide range of carbonyl compound-alcohol systems. Dialkyl ketones have the highest reduction potentials and therefore, the corresponding secondary alcohols have the best reducing capabilities. Carbonyl compounds with low reduction potentials, for example aromatic and aliphatic aldehydes are especially suitable as oxidants in Oppenauer oxidations. Therefore, reaction conditions can be varied according to the nature of the hydrogen acceptor/donor oxidation/reduction potential. Labile substrates can be oxidised at room temperature for several days, whereas heat stable compounds can be heated at reflux, or heated in a sealed tube for only a few hours.

The alkoxide product formed in the MPVO reaction may leave the complex *via* an alcoholysis reaction in which a proton is abstracted from a bulk alcohol molecule. However, if the metal has a greater affinity for the produced alcohol than for the reactant an unfavourable equilibrium exists. In addition, when the metal forms a tight complex with the aldehyde or ketone formed, the catalyst is deactivated. For these reasons and as a result of slow ligand exchange, often stoichiometric amounts of "catalyst" and elevated temperatures are required.

1.4 Modified Aluminium MPVO Catalysts

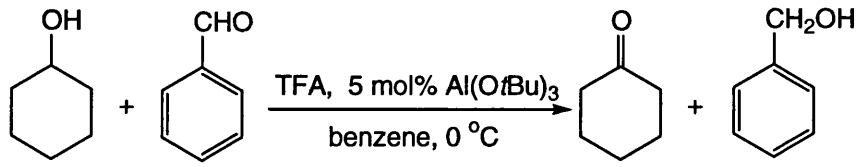
Traditional aluminium catalysts exhibit slow ligand exchange, and consequently there are only a few examples in which aluminium alkoxides have been used in catalytic amounts. An early study by Gál and Kraznai in 1956[65,66] suggested that replacement of 25-30% of the usual aluminium isopropoxide catalyst with chloroaluminium isopropoxide appreciably increases both the rate of MPVO reactions and in addition, the reaction could be performed at lower temperatures (25-40 °C) with few side-reactions (the Tishchenko reaction is a particular problem during the reduction of aldehydes).[67]

Following on from this pioneering study, Rathke and co-workers[68] proposed that the replacement of alkoxy groups on aluminium with more electronegative ligands increased the rate of the MPVO reaction by facilitating co-ordination of aluminium to the carbonyl compound. Furthermore, the addition of a suitable proton acid (HX) to a benzene solution of the aluminium alkoxide should achieve the same aim (Scheme 13).

$$[Al(OR)_3]_n + HX \longrightarrow HOR + [XAl(OR)_2]_n$$

Scheme 13 Formation of proton-aluminium complexes

The most effective additive was found to be trifluoroacetic acid (TFA), present at an acid to aluminium ratio of 0.5. This catalyst-system proved to be far superior to the aluminium alkoxide catalyst alone: in a study of the reaction between cyclohexanol **17** and benzaldehyde **18** (Scheme 14) an 80% conversion was reached in 60 seconds.



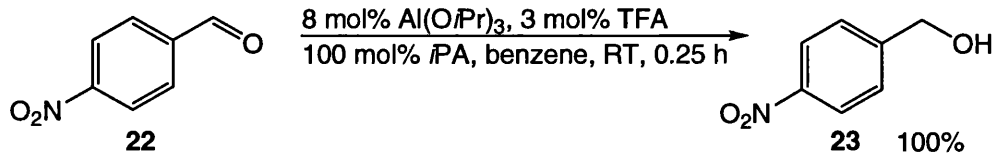
17 **18** **19** **20**

Scheme 14 Modified MPVO Reaction using TFA catalyst

However, synthetic applications of the method are limited by the fact that TFA-aluminium alkoxide mixtures are potent aldol catalysts, especially for simple aliphatic aldehydes.

This work was revived in 1995, when Akamanchi *et al.*[69] reported an accelerated MPV reduction where a 1:1 ratio of aluminium isopropoxide/TFA was found to bring about complete reduction of *para*-nitrobenzaldehyde **22** in the absence of an external hydride source at room temperature within 15 minutes. Thus, in this modified system, aluminium isopropoxide was used as a reagent rather than as catalyst.

A later study[70] further proposed that the same reagent could be used in sub-stoichiometric amounts to efficiently catalyse hydride transfer from isopropanol to substrate in a MPV reduction (Scheme 15).

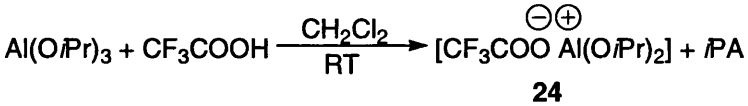


22 **23** 100%

Scheme 15 Modified catalytic MPV reduction of *para*-nitrobenzaldehyde

Under these catalytic conditions, a variety of aliphatic and aromatic substrates were reduced in moderate to excellent yield (20-97%). However, the reduction was much slower when compared to the reactive *para*-nitrobenzaldehyde **22** system and longer reaction times (0.75-24 h) were required.

The scope of the diisopropoxyaluminium trifluoroacetate **24** catalyst was further increased when the reagent was preformed by reacting a solution of aluminium isopropoxide in dichloromethane with TFA, followed by removal of the volatiles *in vacuo*. This provides a dry powder, which can be stored and used conveniently[71] (*c.f.* the complex was previously formed *in situ*) (Scheme 16).

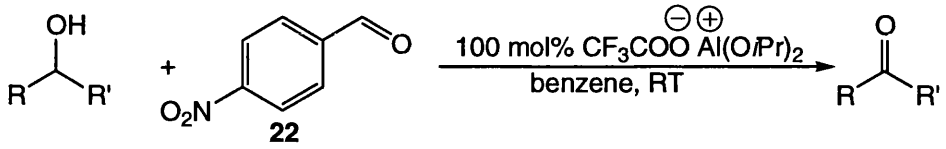


24

Scheme 16 Preparation of diisopropoxyaluminium trifluoroacetate

The diisopropoxyaluminium trifluoroacetate catalyst **24** efficiently reduced a wide-selection of aliphatic and aromatic aldehydes and ketones, including substrates containing problematical basic nitrogen,[58] in excellent yield and within short reaction times. Furthermore, the "off the shelf" catalyst displayed no loss of reactivity towards reduction after three months in a desiccator, thus implying the reagent is stable when stored under anhydrous conditions.

It is unsurprising that diisopropoxyaluminium trifluoroacetate **24** is also able to effectively catalyse the Oppenauer reaction. Drawing considerably on their previous studies, Akamanchi *et al.*[72] demonstrated a highly accelerated Oppenauer system, which employs diisopropoxyaluminium trifluoroacetate **24** as catalyst and a stoichiometric amount of *para*-nitrobenzaldehyde **22** as an irreversible hydride acceptor (Scheme 17).

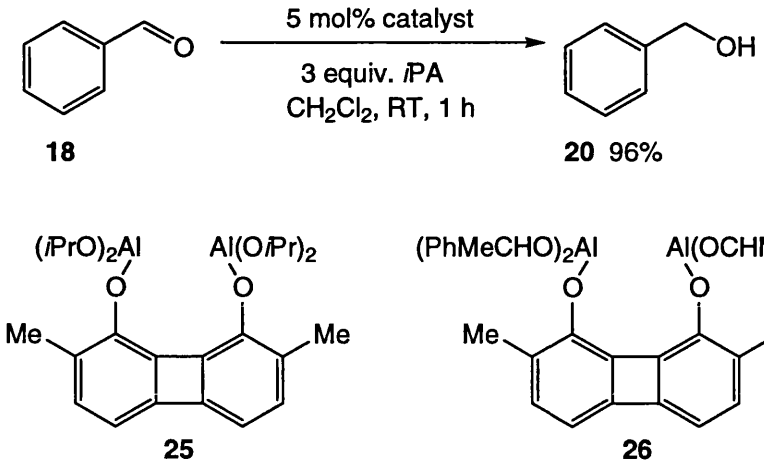


Scheme 17 Modified Oppenauer oxidation of secondary alcohols

Using this modified system a selection of secondary alcohols, both aliphatic as well as benzylic were successfully oxidised to the corresponding ketones in high yield and within a reasonable period of time (0.25-24 h). However, primary alcohols did appear to be inert to oxidation, but, as the authors indicate, this may be useful in selective oxidation procedures.

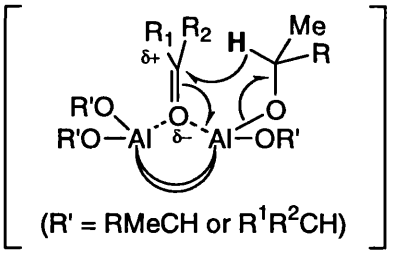
In contrast to the "activated" aluminium alkoxides detailed above, catalytic MPVO reactions have also been achieved by the use of "well-defined" aluminium reagents where the aluminium centres are complexed by multidentate ligands.

This approach is exemplified by the recent work by Maruoka *et al.* who first reported a highly accelerated MPV reduction of carbonyl substrates with a bidentate aluminium catalyst in 1998.[73] Herein the use of the bidentate aluminium catalyst (**25**) (Scheme 18) in the reduction of benzaldehyde **18** produced quantitative benzyl alcohol **20** almost instantaneously at room temperature (*c.f.* a 10% yield using aluminium isopropoxide under identical conditions).



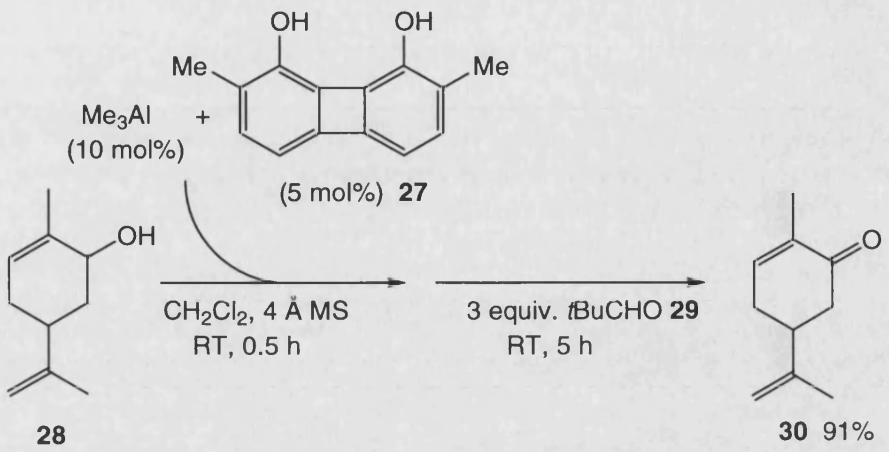
Scheme 18 Catalytic MPV reduction of benzaldehyde

Catalyst **25** can be easily generated *in situ* from 2,7-dimethyl-1,8-biphenylenediol **27**, Me_3Al (2 equiv.), and isopropanol (4 equiv.) and, under similar reaction conditions in addition to aldehydes, both cyclic and acyclic ketones can be reduced equally well. This remarkable efficiency can be ascribed to the double electrophilic activation of carbonyls by the bidentate aluminium catalyst[73] (Scheme 19).



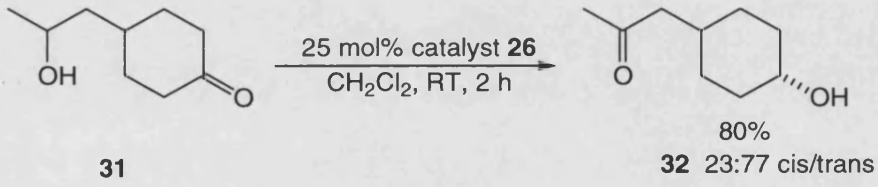
Scheme 19 Double activation of carbonyl group

The present approach is also applicable to a highly accelerated Oppenauer oxidation using both bidentate aluminium catalysts (**25**) and (**26**). This modified, catalytic system effectively oxidises a variety of secondary alcohols to the corresponding ketones. For example, sequential addition of a 1 M Me_3Al solution and carveol **28** to 2,7-dimethyl-1,8-biphenylenediol **27** and subsequent treatment with pivalaldehyde **29** for 5 h at room temperature provided carvone **30** in 91% yield (Scheme 20).



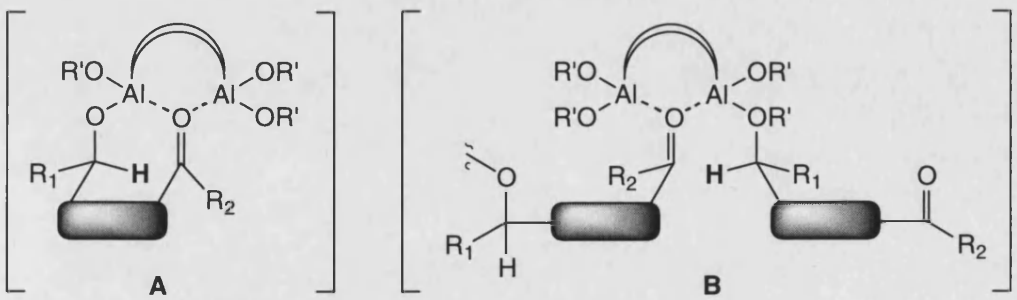
Scheme 20 Catalytic Oppenauer oxidation of carveol with bidentate aluminium catalyst

Bidentate catalyst (**26**) is also able to catalyse an efficient hydrogen transfer within carbonyl compounds possessing *sec*-alcohol functionalities.[74] Herein, the oxidation of the *sec*-alcohol coincides with the concomitant reduction of the carbonyl group. This methodology is illustrated by the oxidation-reduction of hydroxy carbonyl (**31**) (Scheme 21).



Scheme 21 Simultaneous intermolecular MPVO reaction

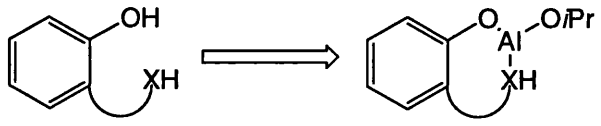
The evidence for an intramolecular hydride transfer in this particular substrate (Scheme 22, pathway A) is precluded by the formation of a small amount of diol product, thus implying the participation of an intermolecular hydride transfer (Scheme 22, pathway B).



Scheme 22 Mechanism of simultaneous functional transformation

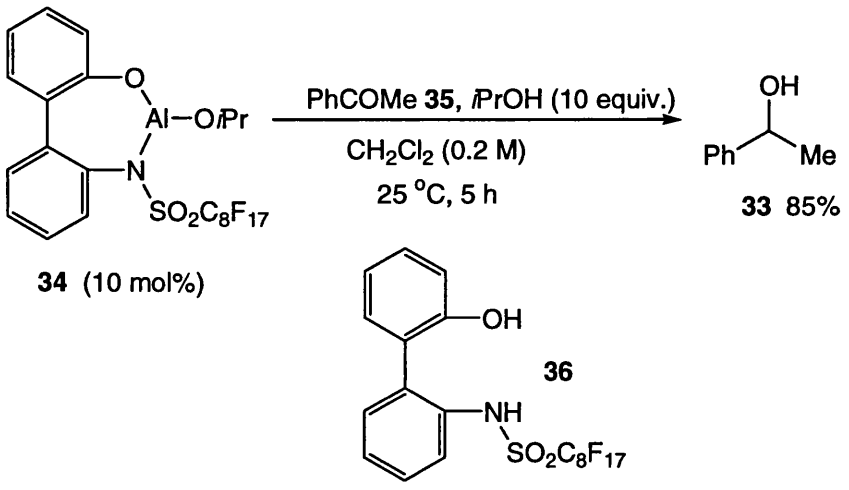
This MPVO reduction/oxidation system is highly chemoselective and can be utilised in the presence of esters, amides, *tert*-alcohols, nitriles and nitro compounds which are all inert to the reaction conditions.

However, this approach requires *sec*-phenethyl alcohol **33** as a hydride donor for smooth reduction of simple acyclic aliphatic ketones and this constitutes a major difficulty (especially in the reduction of aromatic ketones). Therefore synthetic efforts were directed towards a readily accessible aluminium catalyst in which isopropanol could function as a convenient hydride source. Thus, Maruoka *et al.*[75] reported the development of an aluminium catalyst based on the modification of simple aluminium phenoxide *via* introduction of an additional heteroatom-containing group at the *ortho* position of the parent phenol aromatic ring (Scheme 23).



Scheme 23 Development of new aluminium catalyst

Therein it was discovered that the use of a phenolic trifluoromethanesulfonamide group and separately a 2,2'-biphenol-based catalyst each provided moderate yields of *sec*-phenethyl alcohol in a test reduction. Furthermore, combination of these two structural characteristics, and tuning of the perfluoroalkyl group of the sulfonamide moiety afforded an extremely active catalyst species **34** which was able to reduce acetophenone **35** to *sec*-phenethyl alcohol **33** in 85% yield within 5 h (Scheme 24).

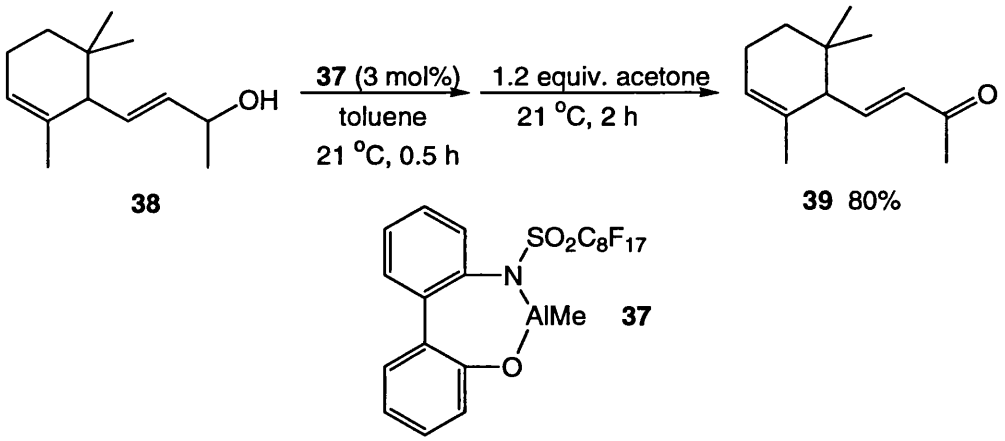


Scheme 24 Efficient catalytic MPV reduction of acetophenone

Catalyst **34** is simply prepared by mixing 10 mol% each of commercially available aluminium isopropoxide and biphenol based ligand **36** in dichloromethane at room temperature, followed by treatment with isopropanol and the ketone to be reduced, thus indicating the intervention of an extremely facile ligand exchange.

A variety of ketones was competently reduced with the optimised catalytic system. As expected cyclic ketones can be reduced instantaneously, and in addition, simple aliphatic and aromatic ketones were also efficiently converted into the corresponding secondary alcohols in excellent yield.

Further improvements to the scope of this excellent catalytic system, the Oppenauer reaction using acetone as a general and convenient hydride acceptor and bidentate pre-catalyst **37** (Scheme 25) was examined.[76]

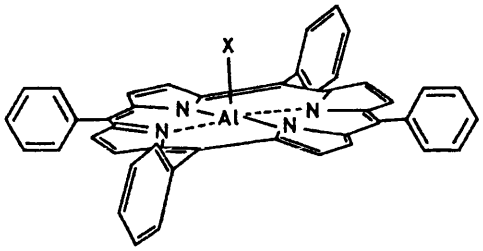


Scheme 25 Catalytic Oppenauer oxidation of terpenoid ketone

This method is exemplified by the oxidation of allylic alcohol (**38**) with only 1.2 equiv. of acetone in the presence of 3 mol% **37** to provide α-ionone **39** in 80% yield in the absence of aldol by-products (Scheme 25). This observation is in sharp contrast to the common situation with aluminium-based Oppenauer oxidation systems, where a 50-200-fold excess of acetone and continuous heating are required to obtain satisfactory results.[46]

Inoue *et al.* reported a catalyst in 1988, which certainly comes under the heading of a "well-defined" aluminium reagent.[77] Herein they reported a novel highly stereoselective hydrogen transfer process catalysed by an aluminium metalloporphyrin, (TPP)AlX (**40**) (TPP = 5,10,15,20-tetraphenylporphinato),

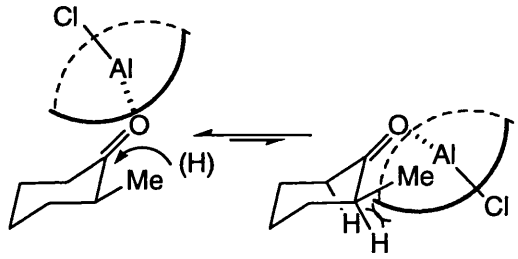
developed for the MPV-type reduction of aldehydes and ketones with isopropanol (Figure 4).



40

Figure 4 Structure of aluminium porphyrin MPV catalyst

A typical example is the diastereoselective reduction of 2-methyl-cyclohexanone with isopropanol (2.5 mmol), in the presence of (TPP)AlCl (0.5 mmol) (**40**; X = Cl) in chloroform at 0 °C. After three hours, the bluish-purple homogeneous solution gradually turned greenish-purple and heterogeneous and subsequent G.C. analysis of the reaction mixture identified two new peaks corresponding to the isomeric mixture of 2-methyl-cyclohexanols **42a,b** (90% conversion). This corresponds to a turnover number with respect to (TPP)AlCl **40** [i.e. product per mol (TPP)AlCl] of 4.5. Interestingly, in the reaction using (TPP)AlCl **40** as catalyst the reduction of the carbonyl group took place stereoselectively (*cis:trans* ratio of 7:93) owing to the pronounced steric effect of the bulky porphyrins ligand (Scheme 26).



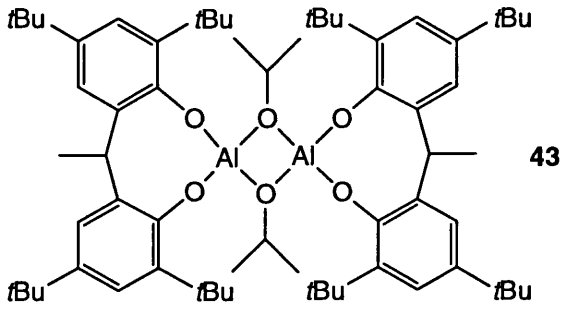
42a **42b**

Scheme 26 Novel chloroaluminium porphyrin diastereoselective reduction

Thus, the substrate carbonyl group is activated by the co-ordination to (TPP)AlCl, leading to facile hydrogen transfer from the alcohol. In the case of the reduction of 2-methylcyclohexanone **42**, preferential formation of complex (**42a**) rather than the alternative (**42b**) (Scheme 26), due to the absence of steric repulsion between the 2,6-axial hydrogens and the porphyrin disc leads to consequent hydrogen transfer

from the less hindered equatorial side, resulting in the predominant formation of *cis*-2-methylcyclohexanol.

The six-membered transition state mechanism for the MPVO reaction is now well accepted, however, the reaction intermediates have never been isolated and thoroughly characterised. Therefore, the crystal structure determination of an MPV reaction intermediate as well as the catalyst would be of immense help in understanding the MPV reaction and thereby modifying the catalytic activity. Thus, the catalytic activity of bidentate catalyst (**43**) (Figure 5) towards MPV hydrogen transfer was studied.[78]

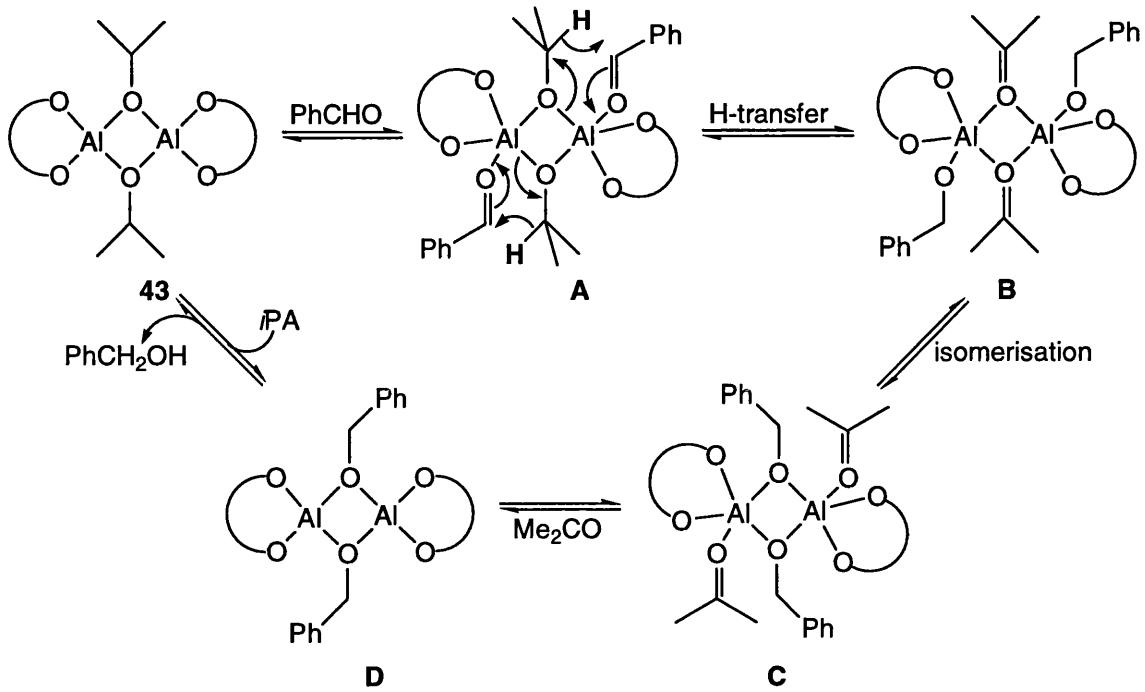


43

Figure 5 Structure of [(EDBP)Al(μ-O*i*Pr)]$_2$ MPV catalyst

Catalyst **43** (10 mol%) was found to catalyse efficiently the hydrogen transfer from isopropanol to aromatic aldehydes, in moderate to excellent yield (60-99%) and within 1 hour at room temperature. This catalytic activity is comparable with the TFA/ aluminium isopropoxide system[71] and, in addition displays no evidence for aldol condensation.

Furthermore, a mechanistic insight can be gained through X-ray structural determination which suggests that an aldehyde molecule co-ordinates to the aluminium centre to form the pentaco-ordinated intermediate **A** (Scheme 27), followed by hydride transfer from the alcoholate to the carbonyl group *via* a six-membered transition state to give the bridging ketone **B**.



Scheme 27 Mechanism of [(EDBP)Al(μ-O*i*Pr)]$_2$ catalysed MPV reaction

Acetone is a much weaker base than a bridging alkoxide, and therefore **B** isomerises rapidly, forming the alkoxy-bridged intermediate **C**, which then loses acetone to give the four-coordinated intermediate **D**. Subsequent ligand exchange with isopropanol regenerates the catalyst **43**, thereby restarting the reaction cycle.

However, catalyst **43** proved to be inactive towards the MPV reduction of ketones, and therefore in an attempt to overcome this problem Lin *et al.* have recently[79] proposed a modified variant of [(EDBP)Al(μ-O*i*Pr)]$_2$. To increase the activity of the aluminium centre, it can be imagined that a more sterically demanding ligand could be introduced in order to make a four-coordinated intermediate possible. Therefore, to fulfil this requirement, the novel aluminium alkoxide [(MMPEP)Al(μ-O*i*Pr)]$_2$ **44** was proposed (Figure 6).

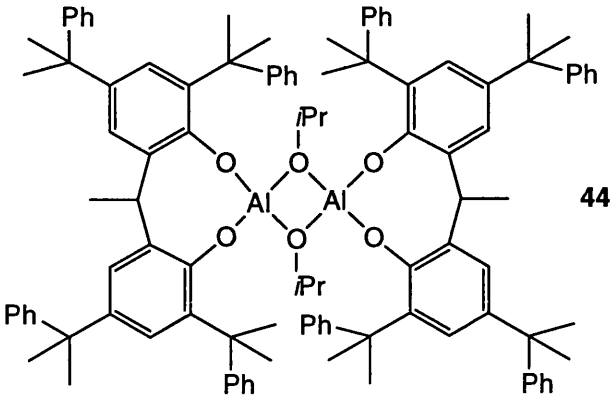
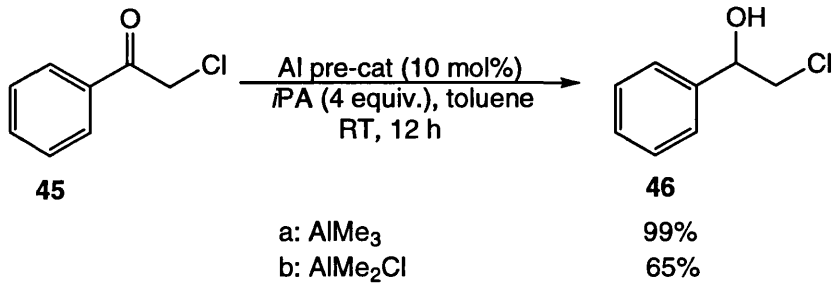


Figure 6 Structure of [(MMPEP)Al(μ-O*i*Pr)]$_2$ MPV catalyst

Preliminary results indicated that [(MMPEP)Al(μ-O*i*Pr)]$_2$ exhibited excellent activity towards both aromatic aldehydes and acetophenones. The reduction of acetophenone **35** to 1-phenylethanol **33** can be achieved within 1 h in the presence of a very low concentration (2.5 mol%) of **44** as catalyst. The mechanism appears to be similar to that reported for [(EDBP)Al(μ-O*i*Pr)]$_2$ **43**, however it appears to proceed through a tetra- rather than a pentaco-ordinate intermediate which is appreciably more sterically hindered than **43** (Figure 5) and therefore, the catalytic rate (and reactivity towards ketones) is much greater.

However, despite these recent advances, a method for the catalytic MPV reduction of organic carbonyls using *simple* aluminium complexes is highly desirable. Therefore, the recent disclosure by Nguyen *et al.*[80] that simple alkyl aluminium reagents are highly active catalyst precursors in the reduction of aldehydes and ketones is an important step forward. These *in situ* generated catalysts show higher activities than those of previously reported complex aluminium systems and in addition, they also demonstrate a high level of stereoselectivity for hydride transfer. These results appear to suggest that the efficiency and the selectivity of the Al-catalysed MPV reaction does not depend solely on the presence of elaborate ligands, but rather they are strongly affected by the aggregation state of the aluminium catalyst (a proposal first noted by Shiner *et al.* in the 1960s).[51,52]

Whereas the classical MPV reduction of carbonyl substrates typically proceeds quite reluctantly at room temperature, the use of simple alkyl aluminium reagents (dimethylaluminium chloride or trimethylaluminium) as pre-catalysts with isopropanol produced primary and secondary alcohols in good yield within 2-12 h (Scheme 28).



45 **46**

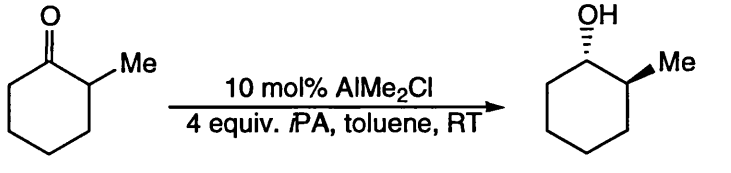
a: $AlMe_3$ 99%
b: $AlMe_2Cl$ 65%

Scheme 28 Catalytic MPV reduction using simple alkyl aluminium reagents

For aromatic aldehyde and ketone substrates, the dimethylaluminium chloride precatalyst tended to be less active than trimethylaluminium, however, the opposite is true for electron-rich ketones. Nevertheless, the excellent catalytic properties of these simple alkyl aluminium complexes are illustrated by the reduction of 2-chloro-1-phenyl-ethanone **45** to 2-chloro-1-phenyl-ethanonol **46** in 99 and 65% yield respectively (Scheme 28).

The authors propose that the remarkable efficiency of the current system is attributed to a low aggregation aluminium alkoxide formed *in situ*, in which few bridging alkoxides are present. It has been postulated that only non-bridging alkoxy groups are able to transfer hydrides to the carbonyl substrates[68] and therefore, highly aggregated aluminium alkoxides would be detrimental to MPV reductions.

Building upon this initial success, the stereoselective hydride transfer properties of this reaction were subsequently investigated. Therein, it was elaborated that these complexes provided comparable or superior diastereoselectivities to aluminium catalyst systems where elaborate ligands with, or without, chiral hydride sources were employed.[73,77] For example, the use of dimethylaluminium chloride precatalyst and isopropanol yields a 20:80 *cis/trans* mixture of 2-methylcyclohexanol **48**, independent of the presence of *meso*-tetra-phenylporphyrin (*vide supra*); it therefore does not appear necessary that ligands are present for either catalyst activity, or stereoselective hydride transfer from chiral secondary alcohols in the MPV reduction catalysed by aluminium alkoxides (Scheme 29).

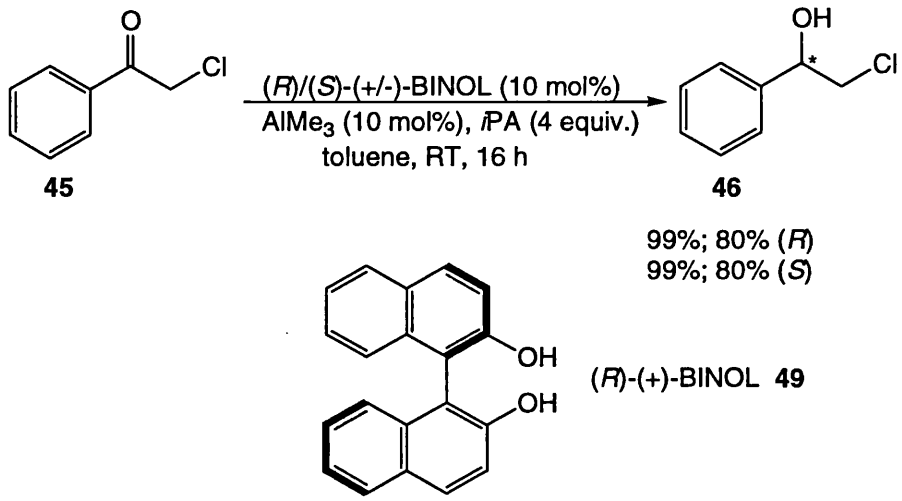


47 **48** 20:80 *cis/trans*

Scheme 29 Stereoselective MPV reduction of 2-methylcyclohexanone

The use of alkyl aluminium reagents to effect MPVO reactions is not without prior precedent. Both Yamamoto[81] and Snider[82] have reported "unexpected" side-reactions attributable to MPVO processes when using alkyl aluminium reagents (diethylaluminium fluoride and dimethylaluminium chloride respectively). In particular, Yamamoto's study highlights an observed high diastereoselectivity for hydride transfer, thus providing further evidence for Nguyen's proposal.

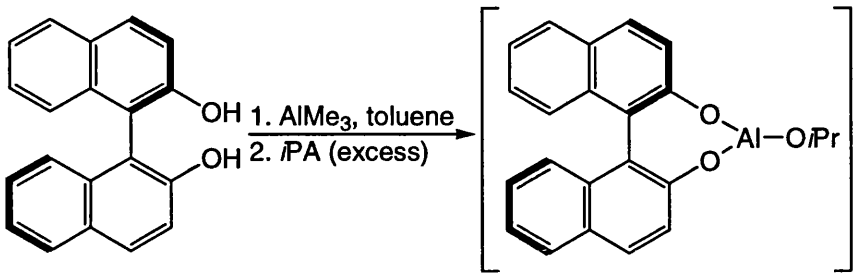
However, somewhat confusingly, Nguyen *et al.* have recently reported[83] an enantioselective, aluminium-catalysed MPV reduction that utilises an enantiopure 2,2'-dihydroxy-1,1'-naphthyl (BINOL)[84] ligand **49** (Scheme 30).



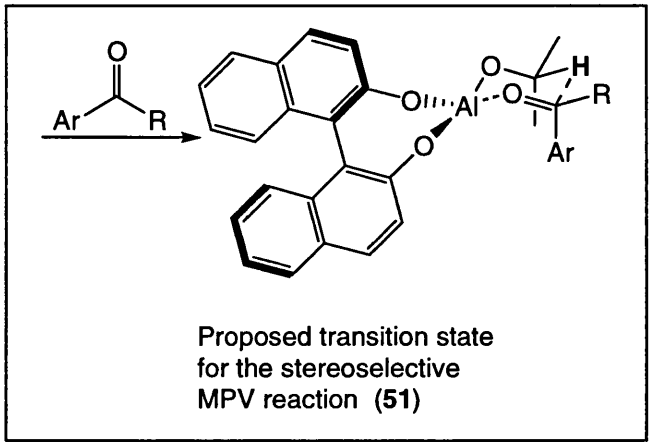
Scheme 30 Asymmetric aluminium catalysed MPV reduction

This simple modification of their earlier work was found to effect smoothly the catalytic reduction of prochiral aromatic ketones in moderate to excellent yield and enantiomeric excess (35-99% yield and 30-80% ee); in this respect, this is the first simple aluminium-based catalyst to exhibit these properties. In general, substrates which are more sterically hindered than propiophenone lead to a lower yield of product, whilst a substrate that is less hindered gives an improved yield, but at a lower enantiomeric excess.

In an analogous manner to the tetraco-ordinate transition state of the classical MPVO reaction, the maximum enanantiomeric excess was achieved when two of the aluminium alkyl groups of trimethylaluminium are protonated by both phenolic protons, to form a 1:1 metal:BINOL complex during the initial catalyst preassembly (Scheme 31).



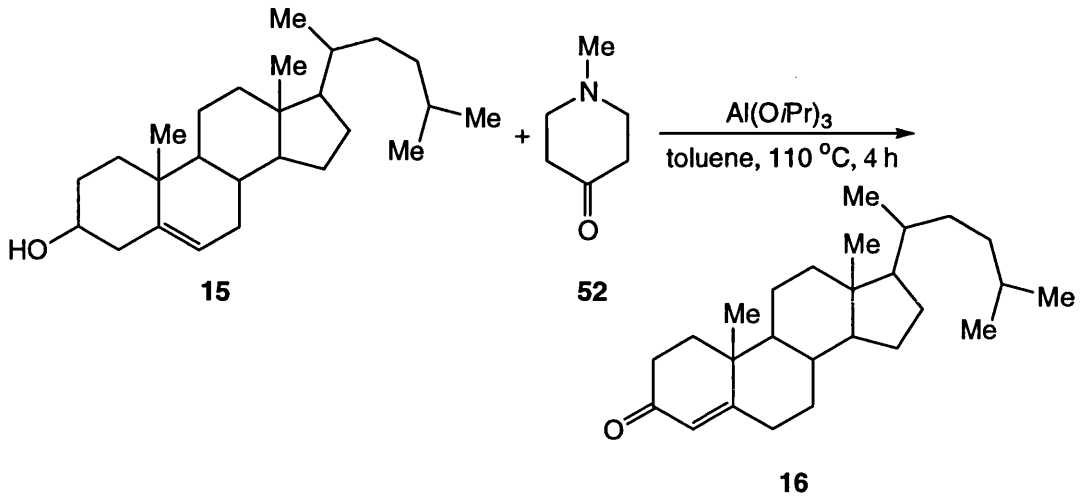
49 Proposed active catalyst (**50**)



Scheme 31 Proposed active catalyst and transition state for the stereoselective MPV reduction

The third aluminium alkyl bond is then protonated by isopropanol, to generate the monomeric [(BINOL)(*i*PrO)Al] active chiral catalyst (**50**) (Scheme 31). This was further confirmed by the use of an isolated sample of [(BINOL)AlMe(THF)], the THF-solvated precursor of [(BINOL)(*i*PrO)Al] **50** from which the active catalyst could be generated for asymmetric reduction.

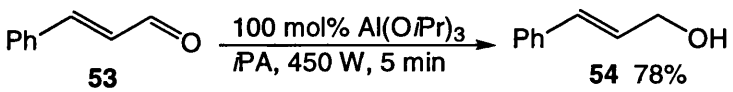
Several attempts have been made to modify the MPVO reaction by substituting acetone with alternative hydride acceptors: for example, acetaldehyde,[85] anisaldehyde,[86] benzaldehyde,[68,87,88] benzophenone,[58,89] cinnamaldehyde,[23,86] cyclohexanone [88], furfural[90] and quinone.[91,92] More recently 1-methyl-4-piperidone **52** has been utilised as a hydride acceptor in the aluminium isopropoxide catalysed oxidation of alcohols.[93,94] The method is illustrated by the oxidation of cholesterol **15** to the corresponding α,β-unsaturated ketone (**16**) in 83% yield (Scheme 32).



Scheme 32 Modified Oppenauer oxidation of cholesterol

This system is advantageous in that excess hydride acceptor and the corresponding alcohol are both readily removed after the reaction by washing the organic layer with dilute aqueous acid. This circumvents the often-encountered difficulty in removing both the excess ketone and the corresponding alcohol, which frequently require steam-distillation, a somewhat tedious procedure not amenable to certain sensitive compounds.

The use of microwave irradiation to effect a modified MPV reaction was reported in 1997 by Barbry and co-workers.[95] Therein, it was suggested that microwave irradiation produces a 20% improvement in yield to that obtained by classical heating; the observed rate enhancement is correlated with superheating of the solvent (isopropanol) under microwave irradiation. Both aliphatic and aromatic aldehydes and ketones are reduced efficiently, in moderate to good yield, within short reaction times. This is illustrated by the reduction of (*E*)-cinnamaldehyde **53** in only 5 minutes (Scheme 33).

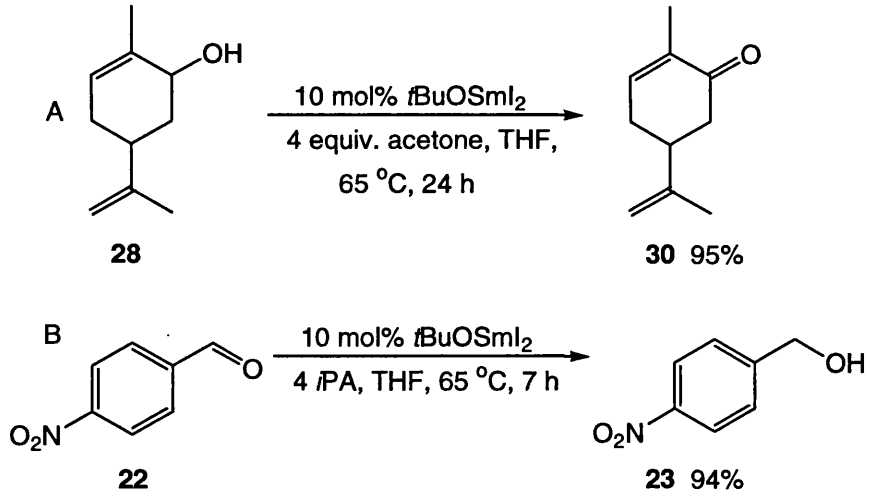


Scheme 33 Reduction of (*E*)-cinnamaldehyde under microwave irradiation

1.5 Lanthanide Catalysed MPVO Reactions

In the last two decades, increasing attention has been paid to the use of lanthanide complexes in organic synthesis.[96,97] For the trivalent lanthanide ions, the 5s and 5p closed shells shield the 4f valence electrons and therefore, the ions have a hard Lewis acidic character and display high ligand exchange rates. In addition, lanthanide (III) ions have co-ordination numbers between 8 and 12 (generally 8 to 9), which allows the use of substoichiometric catalyst loadings.

Kagan *et al.* reported the first use of lanthanum catalysed MPVO chemistry in 1977 during their work towards the pseudo-Barbier alkylation of aldehydes:[98] an unexpected competitive side-reaction was shown to be consistent with an MPV reduction. This work was expanded towards a directed study of samarium and ytterbium catalysed MPV and Oppenauer reactions in 1984,[99] and Sm(O*t*Bu)I_2 subsequently proved to be an excellent MPVO catalyst (Scheme 34).

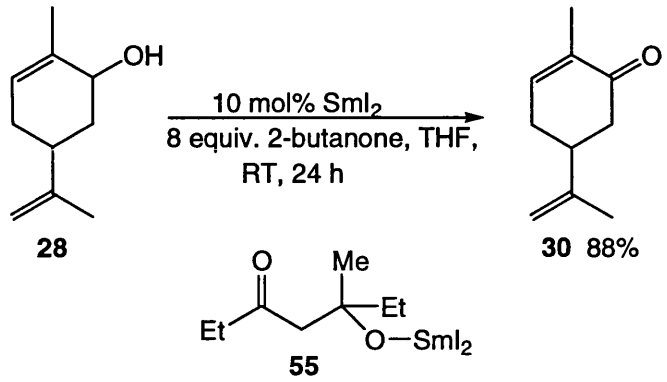


Scheme 34 Sm(O*t*Bu)I_2 catalysed MPV and Oppenauer reactions

The MPV reduction of aliphatic and aromatic aldehydes and ketones (Scheme 34, A) and the Oppenauer oxidation of alcohols (primary, secondary, allylic, aliphatic, aromatic) (Scheme 34, B) proceeded smoothly in the presence of a catalytic amount of Sm(O*t*Bu)I_2. However, both catalyst deactivation by water and the presence of side-reactions (crotonisation of enolisable aldehydes, dehydration reactions of allylic alcohols) does somewhat limit the synthetic scope of this system.

A later study by Kagan *et al.*[100] demonstrated an improved Oppenauer oxidation (Scheme 35) system using SmI_2 as precatalyst; the actual catalyst is proposed to be

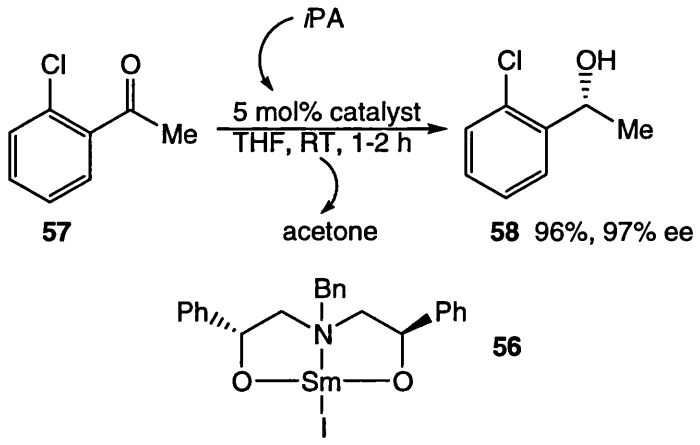
an *in situ* samarium diiodoketolate species **55** (Scheme 35) rather than the expected samarium alkoxide.



Scheme 35 SmI_2 catalysed Oppenauer oxidation of carveol

This oxidation system is more efficient than Sm(O*t*Bu)I_2 catalysis, being performed at room temperature and displays fewer side-reactions, however it does exhibit a narrower scope of activity. Sm(O*t*Bu)I_2 is still the better catalyst for the oxidation of primary alcohols, whilst with the majority of alcohols, in particular allylic alcohols, SmI_2 and butanone is preferable.

Furthermore, Evans *et al.*[101] have recently reported an asymmetric modification of the Sm (III) catalysed MPV chemistry. The 1:1 metal-ligand complex (**56**) (Scheme 36) was demonstrated to efficiently reduce *ortho*-chloroacetophenone **57** to provide the (*R*)-alcohol **58**, in 97% ee and 96% yield.

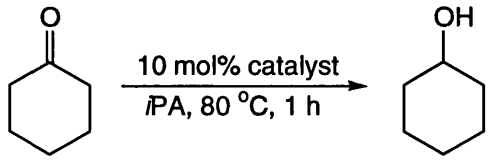


Scheme 36 Asymmetric MPV reduction of *ortho*-chloroacetophenone

Interestingly, catalyst (**56**) is considerably more reactive towards aryl methyl ketones than the *t*BuOSmI_2 complex (*vide supra*), which typically requires a temperature of 60

°C to catalyse the reduction of ketones and provides enantioselectivities which are competitive (68-97% ee) with that of borane reductions, in moderate to excellent yield (43-100%).

In contrast to samarium alkoxides, the lanthanide *tris*-isopropoxides of Nd, Eu, Gd, Dy, Er, Tm, and Yb are very efficient MPVO catalysts. Thus, a recent study by Okano and Kiji[102] compared the reactivity of various lanthanide (III) isopropoxides with aluminium isopropoxide and demonstrated that $Gd(OiPr)_3$ was approximately a thousand times more active (Scheme 37).

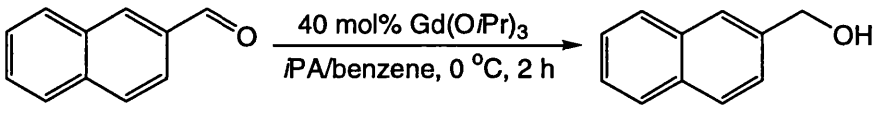


19 **17**

$Gd(OiPr)_3$	99%
$Al(OiPr)_3$	0.5%
$Al(OiPr)_3$ (2 equiv.)	9%

Scheme 37 Comparison of lanthanide and aluminium catalysed MPV reduction

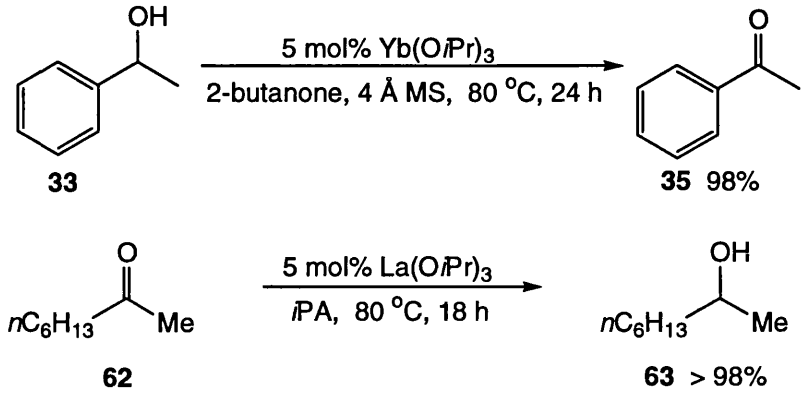
The isopropoxides of Eu, Dy, Er and Tm were also found to be highly active catalysts, however no clear relationship was observed between the catalytic activity of a particular lanthanide and its place in the lanthanide series. Nevertheless, $Gd(OiPr)_3$ was demonstrated to be an excellent catalyst for both the reduction of acyclic and cyclic aldehydes and ketones. In particular, the reduction of aldehydes was extremely fast and reached completion within 15 minutes at room temperature, albeit with a moderate yield (Scheme 38).



59 **60** 62%

Scheme 38 $Gd(OiPr)_3$ catalysed MPV reduction of 1-naphthalenecarboaldehyde

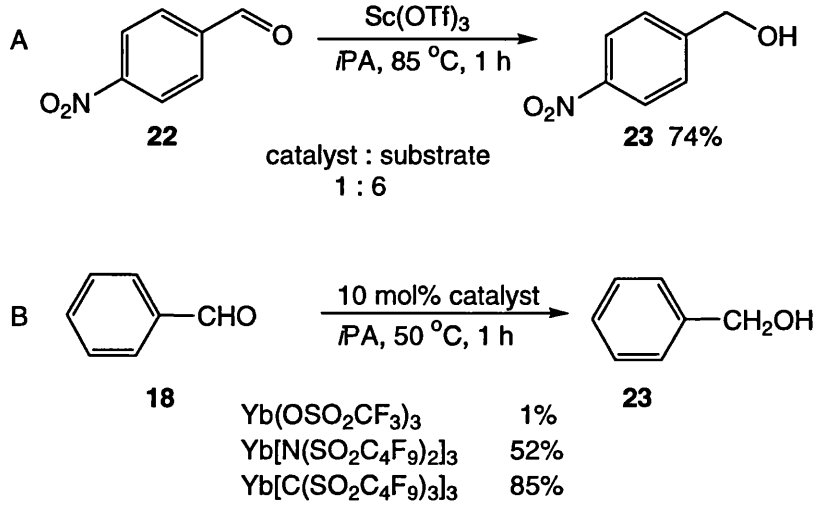
Kagan *et al.*[103] have also investigated the use of simple lanthanide alkoxides in the MPVO reaction; recently developing a novel preparation of the isopropoxides of lanthanum, cerium, samarium and ytterbium. Ytterbium appeared to be the most active catalyst for the oxidation of 1-phenyl-1-ethanol **33**, whilst lanthanum displayed the greatest activity towards the reduction of 2-octanone **62** (Scheme 39).



Scheme 39 Ln (III) isopropoxide catalysed MPVO reactions

However, with regard to Kagan's earlier work (*vide supra*) using *t*BuOSmI$_2$, it is interesting that Sm(O*i*Pr)$_3$ was delineated to catalyse both the Oppenauer (70%) and MPV (98%) reactions effectively. This suggests that the active catalyst *is* a samarium alkoxide and not a samarium ketolate as previously reported.

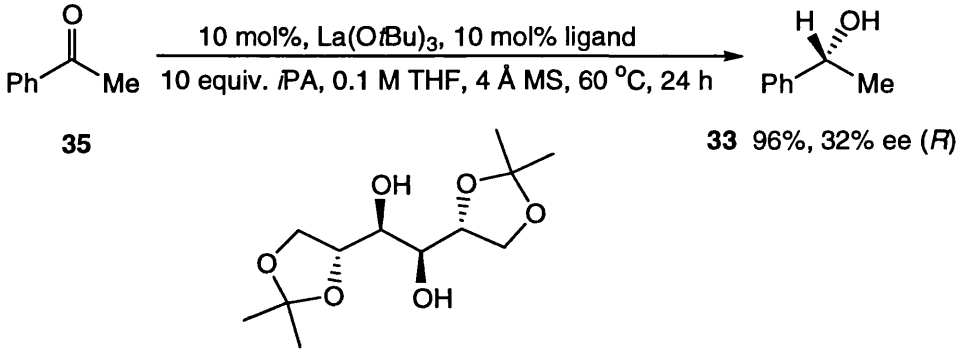
Castellani *et al.*[104] have examined the effect of the counterion towards lanthanide MPVO chemistry and compared the reactivity of La (III), Lu (III), Y (III), and Sc (III) chlorides, perchlorates, and trifluoromethanesulfonates. Furthermore, scandium (III), which has seldom been employed before as a homogeneous catalyst for organic reactions, appeared to be an efficient MPV catalyst for the reduction of aldehydes and ketones (Scheme 40, A). However, the synthetic utility of this system is compromised, by its high cost, moisture sensitivity and the tendency for etherification of the product alcohol with isopropanol.[105]



Scheme 40 Scandium and ytterbium catalysed MPV reductions

Nevertheless, Yamamoto *et al.*[106] have also reported similar lanthanide catalysed MPV reductions (Scheme 40, B). Therein, ytterbium methide and amide complexes were able to reduce benzaldehyde **18** effectively, in moderate to good yield within a short reaction time, whilst ytterbium triflate is essentially inert. However, etherification of the product to provide benzyl isopropyl ether was again observed as a by-product.

Lanthanide complexes have additionally been used to obtain moderate chiral induction in an asymmetric MPV reduction.[107] Thus, a chiral catalyst prepared *in situ* through the addition of dihydroxy ligand (**64**) to a solution of lanthanide *tert*-butoxide in isopropanol was able to reduce acetophenone in 32% ee (Scheme 41).

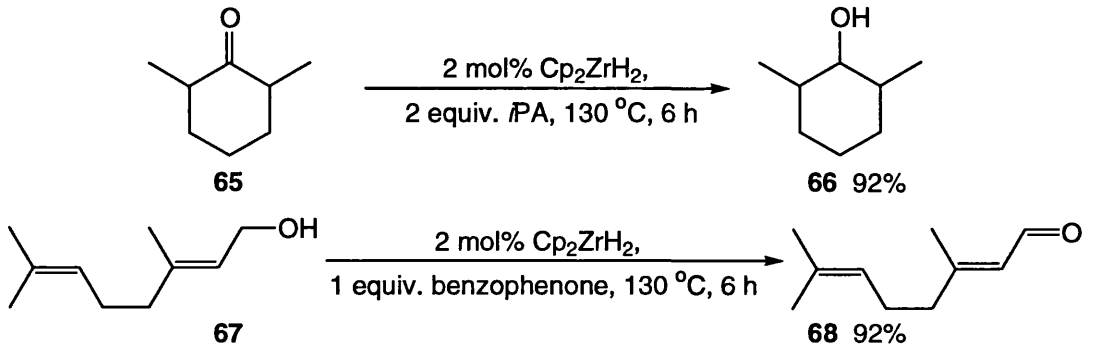


1,2:5,6-di-*O*-iso-propylidene-D-mannitol **64**

Scheme 41 Asymmetric lanthanide (III) alkoxide catalysed MPV reduction

1.6 Zirconium and Hafnium catalysed MPVO Chemistry

MPVO chemistry is of course, not limited to the main group elements. Thus, Ishii and Ogawa pioneered the use of zirconium complexes to effect MPVO reactions in 1986.[108] Thus, bis(η^5-cylopentadienyl)zirconium dihydride, Cp_2ZrH_2 was demonstrated to be an excellent catalyst for both the MPV reduction and the Oppenauer oxidation (Scheme 42) of aromatic and aliphatic substrates, albeit at a somewhat elevated temperature.

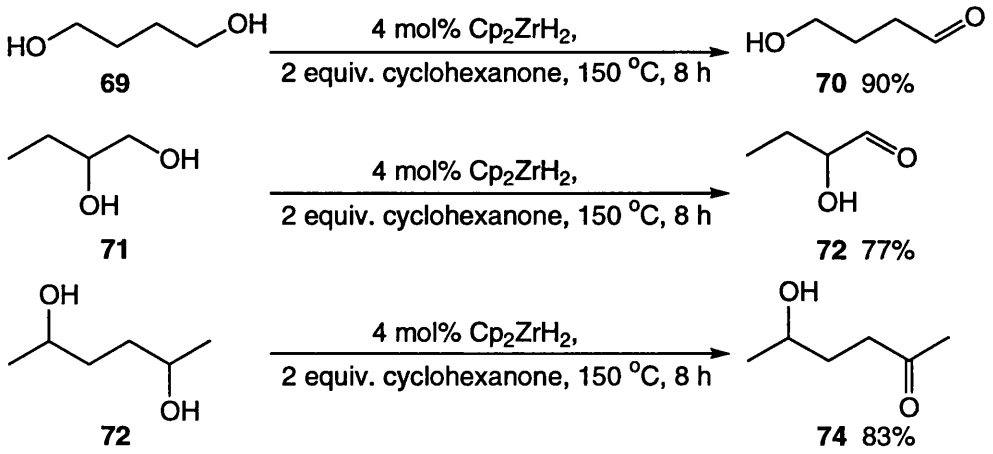


Scheme 42 Zirconium catalysed MPVO reactions

The general trend for the ease with which zirconocene MPV reduction occurred appeared to decrease in the order aldehydes > aromatic > alicyclic > aliphatic ketones. Therefore, in the reduction of compounds containing multiple carbonyl groups, a particular carbonyl will be reduced preferentially by this method (*vide infra*).

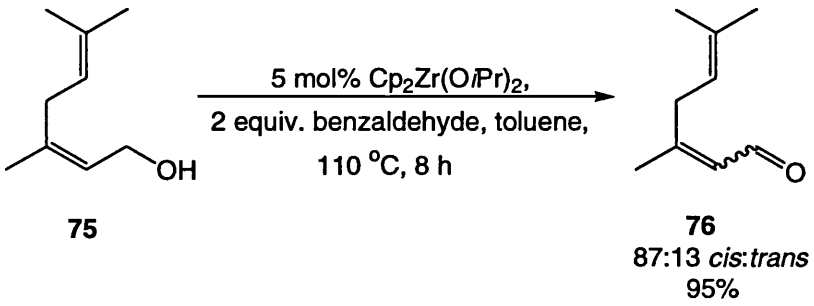
An interesting corollary to this work was that the catalyst (the active catalyst is proposed to be the incipient zirconium alkoxide) could be recycled from the reaction mixture with no significant loss of activity.

A later study[109] extended the scope of the zirconium catalysed Oppenauer reaction to the chemoselective oxidation of primary alcohol functions in diols. Thus, a number of diols were oxidised smoothly to the corresponding hydroxy aldehydes in excellent yield and without the formation of dialdehydes (Scheme 43).



Scheme 43 Chemoselective Oppenauer oxidation of diols

The zirconium complexes, bis(η^5-cylopentadienyl)zirconium dihydride and bis(η^5-cyclopentadienyl)zirconium diisopropoxide, $Cp_2Zr(OiPr)_2$, appear ideally suited to the selective oxidation of allylic alcohols to α,β-unsaturated carbonyl compounds.[110] For example, the primary allylic terpenoid alcohols, geraniol and nerol **75** are efficiently oxidised to the corresponding α- and β-citrals (**76**) which are essential compounds in the perfume industry (Scheme 44).

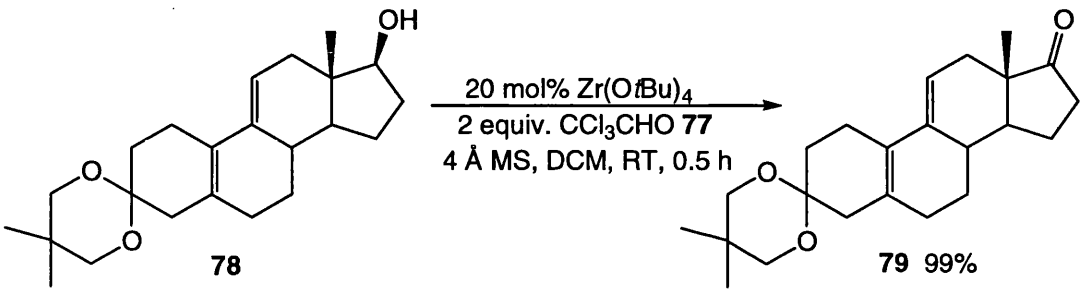


Scheme 44 Zirconium catalysed Oppenauer oxidation of nerol

It is interesting to note that the proposed *in situ* active catalyst bis(η^5-cyclopentadienyl)zirconium diisopropoxide when preformed, demonstrates comparable reactivity to bis(η^5-cylopentadienyl)zirconium dihydride.

Although Ishii reported that zirconium tetraisopropoxide, $Zr(OiPr)_4$, was a poor Oppenauer catalyst in comparison with the corresponding zirconocene derivatives, recent work by Krohn *et al.*[111] has demonstrated that with zirconium tetra-*tert*-butoxide, $Zr(OtBu)_4$, a mild catalytic Oppenauer reaction *is* possible using chloral **77** as the hydride acceptor. With analogy to dimethylaluminium chloride MPVO chemistry, the zirconium complex is monomeric in solution and therefore the ligand

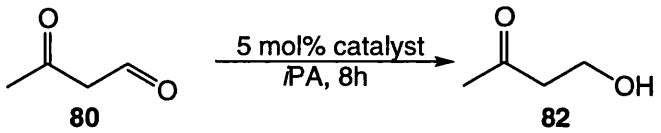
exchange is very rapid, thus explaining the high catalytic activity observed. Both sterols (**78**) (Scheme 45), primary and secondary allylic and saturated alcohols, were converted to the corresponding carbonyl compounds (**79**) in high yield (67-99%) and within short reaction times (0.5-9 h).



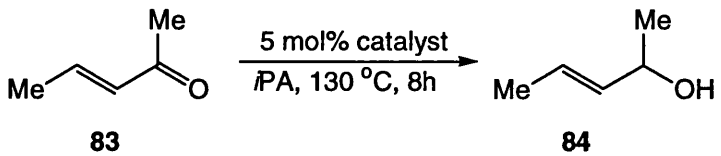
Scheme 45 Zirconium *tert*-butoxide catalysed MPV oxidation

The commercially available chloral **77**, whilst acting as an excellent hydride acceptor due to its high redox potential, has the additional practical advantage that any excess can be removed through a simple aqueous extraction of the chloral hydrate (*r.f.* 1-methyl-4-piperidone **52** *vide supra*).

Unsurprisingly, zirconocene complexes and the analogous hafnium (and to a lesser degree titanocene) derivatives are also able to catalyse the corresponding MPV variants of the reactions detailed above.[112] Consequently, the chemoselective reduction of polycarbonyl compounds (**80**) to hydroxy carbonyls (**82**) and the selective 1,2-reduction of α,β-unsaturated carbonyl compounds (**83**) proceeded in excellent yield under both zirconium and hafnium catalysis (Scheme 46).



Cp_2ZrCl_2, 130 °C, 43%
Cp_2HfCl_2, 80 °C, 90%

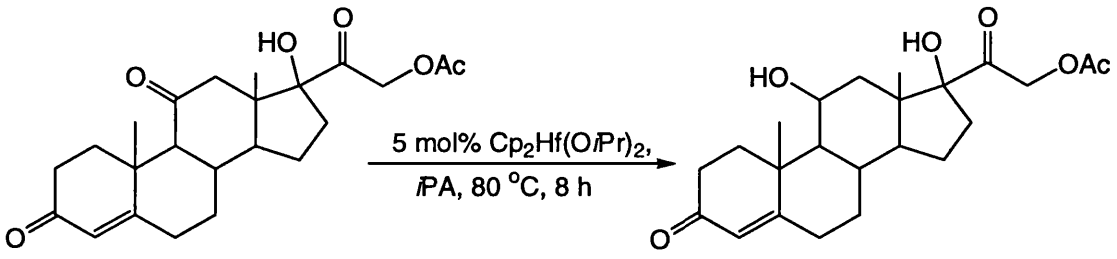


Cp_2ZrH_2 94%
Cp_2HfH_2 96%

Scheme 46 Zirconocene and hafnocene MPV reductions

However, hafnocene complexes do appear to be superior to the corresponding zirconocene complex, which is attributed to the relative strengths of the metal-chlorine bond. Thus, the hafnium-chlorine bond is appreciably weaker than the zirconium-chlorine bond[113] and therefore it is easier to form the *in situ* metal alkoxide key-intermediate.

An excellent demonstration of hafnocene MPV reduction is provided by the chemoselective reduction of the steroidal ketone Δ^4-cortin-3,11,17-trione 20-acetate **85** (Scheme 47).

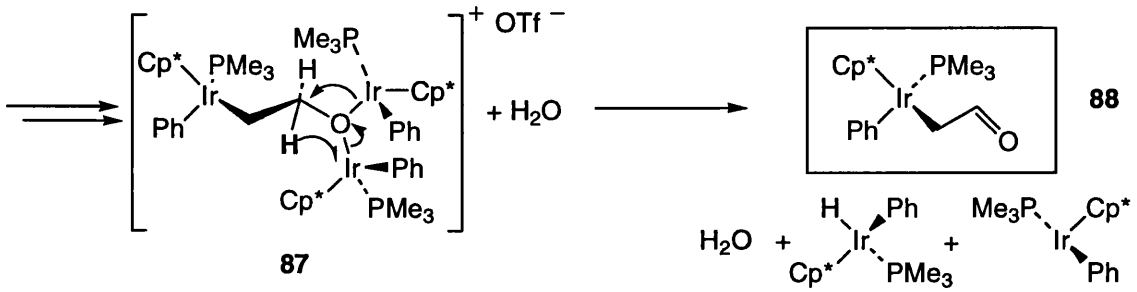


85 **86** 44%

Scheme 47 Hafnocene MPV reduction of Δ^4-cortin-3,11,17-trione 20-acetate

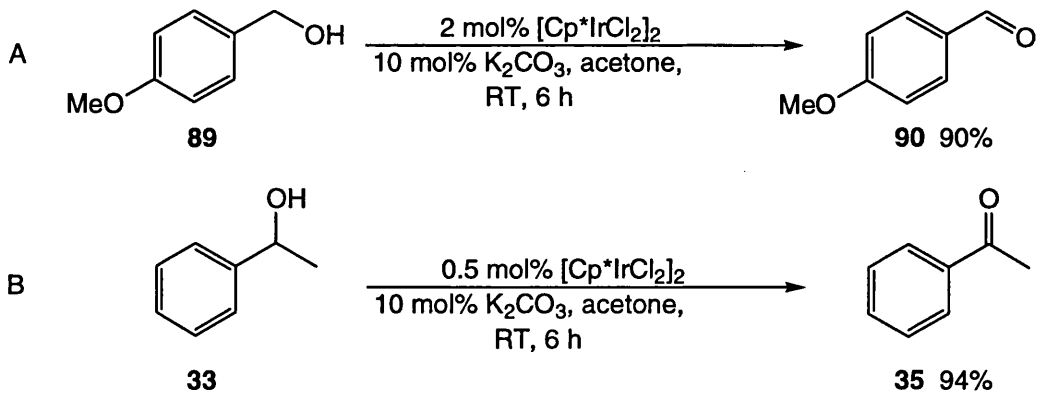
1.7 Miscellaneous MPVO Reactions

There are several examples in the literature of either serendipitous or highly *unusual*[114] MPVO reactions. These are illustrated by a recent study reported by Bergman and co-workers.[115] During work towards elucidating the mechanism of addition of an Ir-OH bond to ethylene, it was reported that during the catalytic cycle an iridium alkoxide was found to take part in an MPV-like hydride transfer (Scheme 48) from the electron-rich alkoxide **87** to the Ph[Ir]$^+$ fragment.



Scheme 48 Iridium catalysed MPV-like hydride transfer

The reverse process, i.e. an iridium-catalysed Oppenauer oxidation, has also been recently disclosed.[116] Therein, Yamaguchi *et al.* reported that catalytic amounts of $[Cp^*IrCl_2]_2$ and K_2CO_3 efficiently converted primary (**89**) and secondary alcohols into the corresponding aldehydes (**90**) and ketones with high selectivity and in good yield (Scheme 49, A).

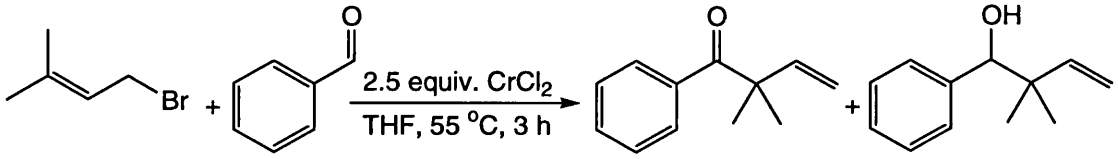


Scheme 49 Oxidation of *para*-methoxybenzyl alcohol with $[Cp^*IrCl_2]_2$

Furthermore, in contrast to primary alcohols (**33**), secondary alcohols could be oxidised using a very small catalyst loading (0.50 mol% Ir) to provide the corresponding ketones (**35**) in excellent yield (Scheme 49, B).

Although the mechanism has not been fully elucidated, it appears to follow the route suggested by Backväll[117,118] (Scheme 7, path A), whereby acetone inserts into the Ir-H bond to afford a metal isopropoxide, which then releases the product *via* β-hydride elimination.

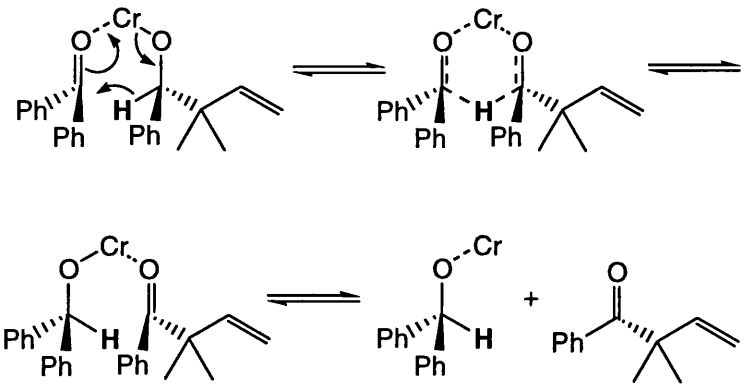
A further transition metal catalysed MPVO reaction was recently disclosed by Wessjohann and co-workers.[119] Herein, oxidation products, predominantly allyl ketones, were observed during Hiyama-Nozaki[120] reactions of allylchromium with aldehydes where the expected products are homoallylalcohols. This is illustrated by the reaction of dimethylallyl bromide **91** with benzaldehyde **18** mediated by chromium dichloride (Scheme 50).



91 1 equiv. **18** 3 equiv. **92** 83% **93** 8%

Scheme 50 Oxidative Hiyama-Nozaki reaction

The formation of ketone products was proposed to occur through an Oppenauer-type mechanism (Scheme 51). As noted by the authors, the simultaneous presence of an alkoxide, an aldehyde and a multivalent metal ion (as a potent Lewis acid) together with the expulsion of oxygen suggests optimal conditions for an Oppenauer-type oxidation reaction.

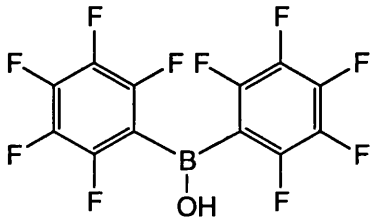


Scheme 51 Chromium-mediated MPVO reaction

The amount of oxidation is strongly dependent upon the substitution pattern of the reaction partners and the reaction conditions; in general, alkyl substitution at the allylic γ- and β-position, excess aldehyde (hydride source), higher temperatures and

aldehydes with electron-donating substituents, all favour the subsequent formation of allyl ketones.

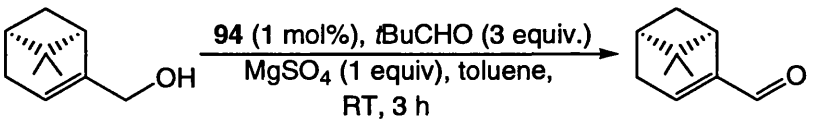
However, Yamamoto *et al.*[121] delineated perhaps the most interesting recent MPVO system, bis(pentafluorophenyl)-borinic acid **94** (Figure 7), which displays excellent Oppenauer catalyst activity towards primary and secondary allylic and benzylic alcohols.



94

Figure 7 Structure of bis(pentafluorophenyl)-borinic acid Oppenauer catalyst

The generality and scope of the borinic acid (**94**)-catalysed Oppenauer oxidation was explored using several different primary and secondary alcohols. Furthermore, it was demonstrated that excellent conversions to α,β- enals (**96**) and enones could be achieved under very mild conditions and within short reaction times (Scheme 52).



95 **96** > 99%

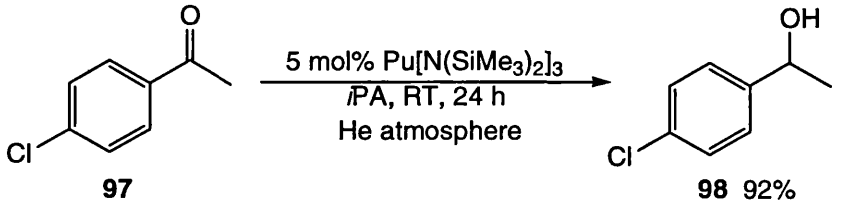
Scheme 52 Borinic acid catalysed Oppenauer oxidation

The authors propose that mechanistically, the reaction is similar to conventional Oppenauer oxidations catalysed by metallic alkoxides, which have a basic character. However the strong Lewis acidity of (**94**) remarkably enhances the co-ordination of the carbonyl acceptor with the metal, thus providing the increased driving force for the Oppenauer oxidation.

MPVO reactions have also been the focus of recent work within the Los Alamos National Laboratories in New Mexico, U.S.A.[122] Thus the reactivity of Th(IV), U(III), U(IV), Pu(III) and Pu(IV) isopropoxide towards the MPV reduction of ketones by isopropanol was examined. Studies of actinide compound reactivity toward organic-based materials represent an important area of actinide-element research. This is

due to the fact that there are many instances in which actinides come into contact with potentially reactive functional groups; waste disposal for example.

The actinide alkoxides were effectively prepared *in situ* from the lanthanide tris(amido) pre-catalysts (Scheme 53). Furthermore, plutonium (III) isopropoxide exhibited similar or slightly enhanced reactivity towards MPV reduction of aliphatic and aromatic ketones when compared to lanthanide alkoxide complexes. However, uranium (III) and the An (IV) isopropoxide complexes do not exhibit any appreciable catalytic activity, even at elevated temperatures. This is therefore consistent with assigning reactivity to be analogous to zirconium (IV) chemistry under these conditions.

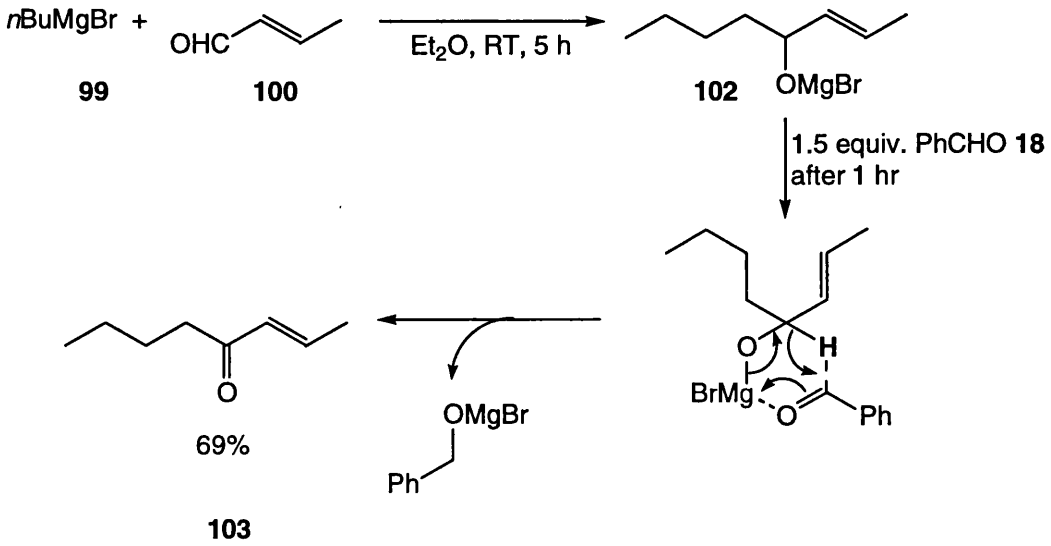


97 **98** 92%

Scheme 53 Plutonium (III) catalysed MPV reduction of *para*-chloroacetophenone

Although the use of magnesium ethoxide as a reagent to accomplish the reduction of benzaldehyde **18** was first recognised by Meerwein and Schmidt in 1925,[22,123,124] the synthetic utility of the magnesium catalysed Oppenauer reaction was until recently virtually unexplored. Therefore the discovery by Byrne and Karras[87] that the oxidation is facile when employing an efficient hydride acceptor, for example benzaldehyde **18**, was an important achievement.

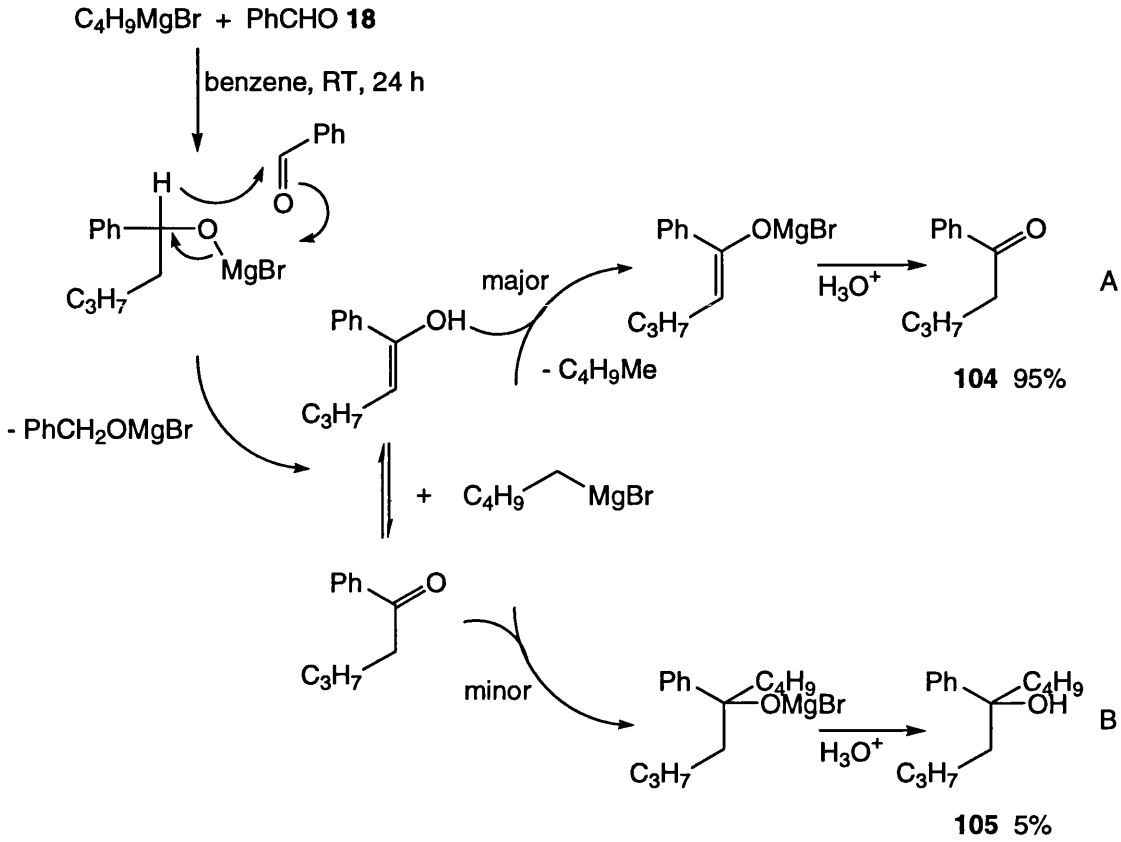
The major advantage of the magnesium-Oppenauer oxidation is that the powerful synthetic utility of the Grignard reaction is used to obtain ketones in a one-pot domino alkylation-oxidation sequence (Scheme 54).



Scheme 54 Magnesium catalysed Oppenauer oxidation of secondary alcoholate

Thus, the sequential addition of benzaldehyde **18** to a solution of Grignard reagent (**99**) and but-2-enal **100**, after the initial alkylation reaction is complete, leads to a synthetically useful yield of 2-octen-4-one **103** within 5 hours. This conversion of primary alcohols into the corresponding aldehydes is equally successful; being accomplished by initial alcohol deprotonation with ethylmagnesium bromide, followed by addition of benzaldehyde.

Vlassa *et al.* have recently proposed[125] an extension to the magnesium Oppenauer oxidation whereby the same aldehyde (**18**) is used as both substrate *and* hydride acceptor (Scheme 55, path A)

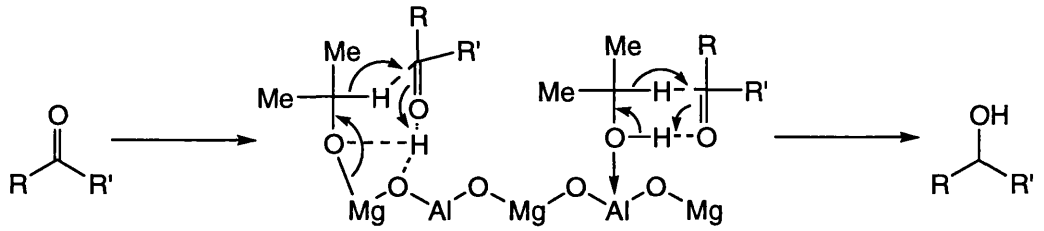


Scheme 55 Synthesis of ketones *via* magnesium mediated Oppenauer reaction

Excellent yields of ketone (**104**) were obtained (70-95%) which appeared to be unaffected by the hydride acceptor ability when using benzene as solvent. The presence of tertiary alcohol (**105**) in the reaction mixture is consistent with a minor competitive reaction of Grignard regent with ketone (Scheme 55, path B).

1.8 Heterogeneous MPVO Catalysts

A further class of catalysts are not elaborated in this review: heterogeneous MPVO complexes (Scheme 56). First reported by Posner *et al.* in 1976,[126] heterogeneous MPVO catalysts, which utilise a solid metallic surface (commonly alumina or zeolites), have been extensively reviewed by Huskens *et al.*[47,127] and although these catalysts often display good stereoselectivity, a large amount of catalyst is frequently required (typically 1-2 g Al_2O per mmol substrate) to achieve high conversions and therefore the synthetic scope is somewhat limited.



Scheme 56 Proposed mechanism of the MPV reduction over Mg-Al hydrotalcite

1.9 Meerwein-Ponndorf-Verley Alkylation

However perhaps Maruoka *et al.* reported the most interesting recent MPVO reaction.[128] Although the facile hydride transfer mechanism for the MPVO reaction is well accepted (Figure 8, A), the corresponding alkylation, i.e. MPV alkylation, has never been realised mainly because of the inertness of alkyl transfer (Figure 8, B).

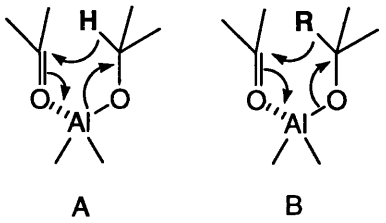
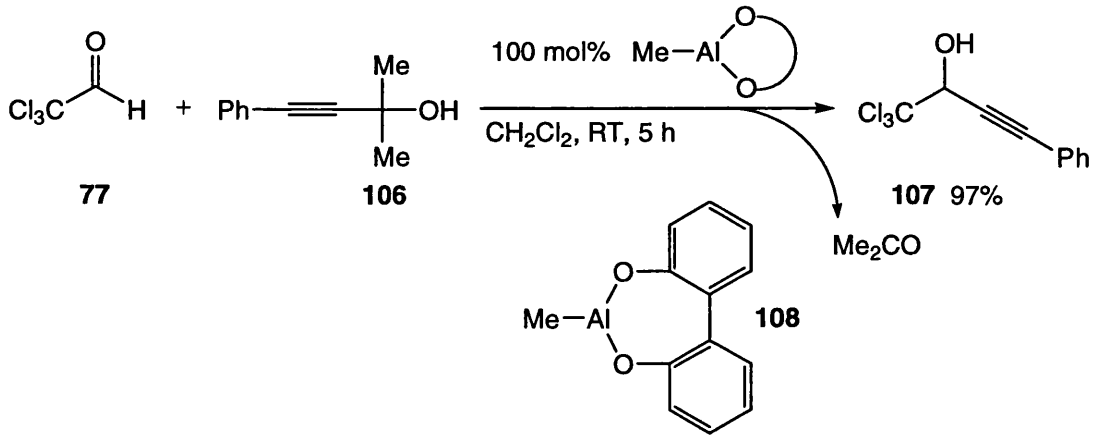


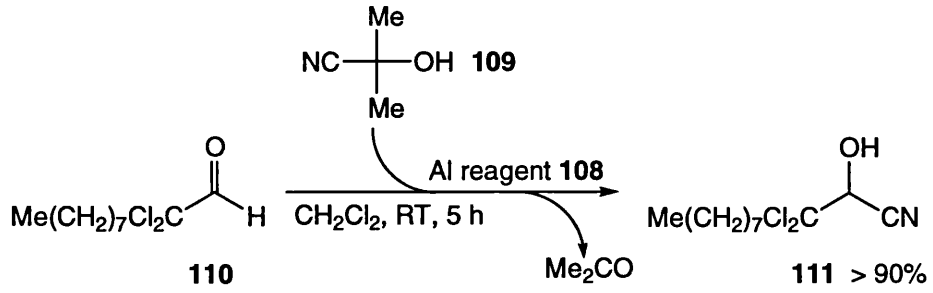
Figure 8 MPV reduction *vs.* MPV alkylation

Thus, Maruoka demonstrated that a series of reactive aldehydes could be transformed into the corresponding secondary propargylic alcohols (**107**) under mild chemoselective MPV alkynylation conditions when using the modified aluminium reagent (**108**) (Scheme 57).



Scheme 57 Aluminium catalysed MPV alkynylation of chloral

This methodology was also demonstrated to be applicable to the cyanation of aldehydes with commercially available acetone cyanohydrin as cyanide source; for example, treatment of 2,2-dichlorodecanal with acetone cyanohydrin **109** under the influence of aluminium reagent (**108**) afforded the corresponding cyanohydrin (**111**) in excellent yield (Scheme 58).



Scheme 58 Aluminium catalysed MPV cyanation of aldehydes

1.10 References

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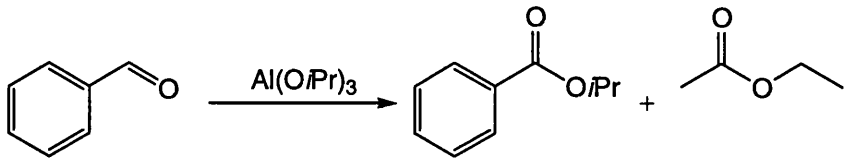

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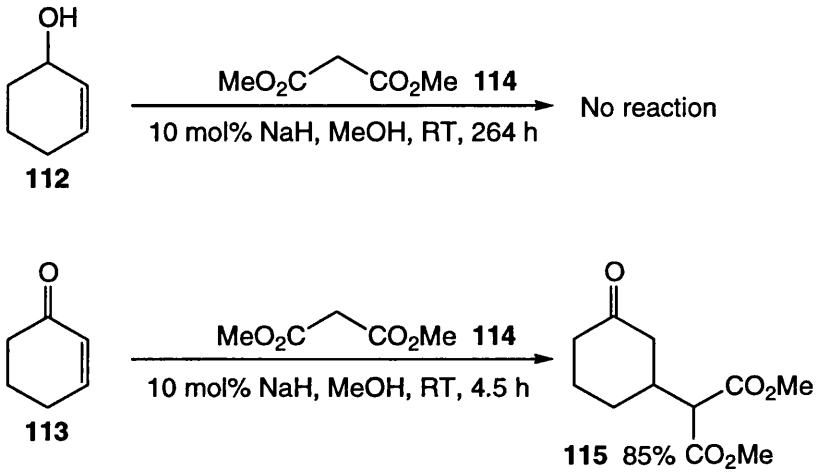
Chapter 2

2.0 Results and Discussion I

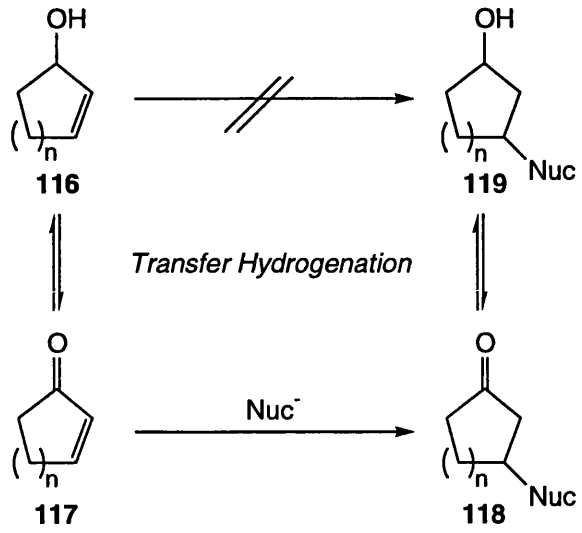
2.1 Project Overview

As a general principle, nucleophiles are able to add to electron-deficient alkenes, but are reluctant to react with electron-rich alkenes.[1] This is readily demonstrated by a comparison of the reactivity of 2-cyclohexen-1-ol **112** and 2-cyclohexen-1-one **113** towards the nucleophile derived from dimethyl malonate **114** (Scheme 59).



Scheme 59 Comparison of allylic alcohol and enone reactivity towards nucleophiles

With increasing worldwide interest in domino and cascade reactions,[2-7] we have considered the possibility of temporarily converting the unreactive allylic alcohol (**116**) into the electronically activated α,β-unsaturated ketone (**117**). The electronically activated substrate (**117**) could then undergo a facile conjugate addition and, if the alcohol functional group is subsequently restored (**119**) in a *one-pot* procedure this would lead to an indirect addition of nucleophiles to allylic alcohols (Scheme 60). This methodology has been termed **Catalytic Electronic Activation** (CEA).



Scheme 60 Catalytic Electronic Activation of an allylic alcohol

The usual procedure to accomplish this reaction would be *via* the stepwise synthesis of the individual intermediates through to the target molecule. However, the proposed scheme is much more efficient in that several separate chemical steps occur in a consecutive fashion without changing the reaction conditions, or adding reagents. It is obvious that this type of reaction would allow the minimisation of waste; compared to the stepwise process, the amount of solvent, reagents, adsorbents and energy used would be dramatically decreased. Therefore, this reaction sequence is both ecologically and economically attractive.

For this one-pot approach to be successful, the following criteria must be met:

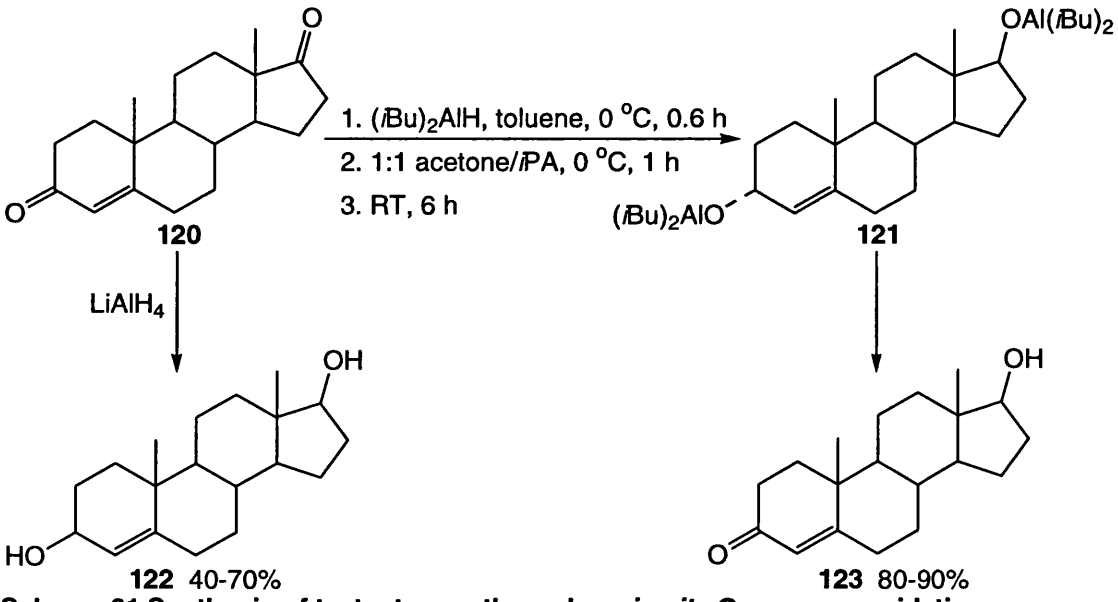
- **The interconversion of alcohol and ketone must be rapid and reversible**
- **The method for alcohol/ketone interconversion must be compatible with the conjugate addition**

The success of the overall CEA principle depends on these requirements.

The most straightforward process for alcohol/ketone interconversion is arguably transfer hydrogenation and there is plenty of scope in this area for choice of catalyst.[8-12] However, for some rhodium and ruthenium catalysts double-bond migration of allylic alcohols is a known process, affording the saturated ketone by isomerisation (Appendix 1).[13,14] It is for this reason that we initially chose to explore aluminium (MPV catalysts) for their ability to effect transfer hydrogenation between 2-cyclohexen-1-ol **112** and ketone (**115**).

However, a significant drawback to this approach is highlighted by the paucity of MPVO domino reactions within the scientific literature. Whilst limited examples of lanthanide[15], samarium,[16] titanium[17] and zirconium[18,19] catalysed MPVO-type tandem processes have been recently reported, only five examples of aluminium catalysed reactions (*vide infra*) were elucidated during an extensive literature search. Nevertheless, this could merely highlight the perceived synthetic weakness of MPVO reactions towards modern Organic Chemistry.

The first *in situ* Oppenauer oxidation was reported by Eder in 1976.[20] Therein, during an attempted synthesis of testosterone **123** it was discovered that the carbonyl precursor, 4-androsten-3,17-dione **120**, was prone to over-reduction with lithium aluminium hydride to give the diol product (**122**) (Scheme 61).

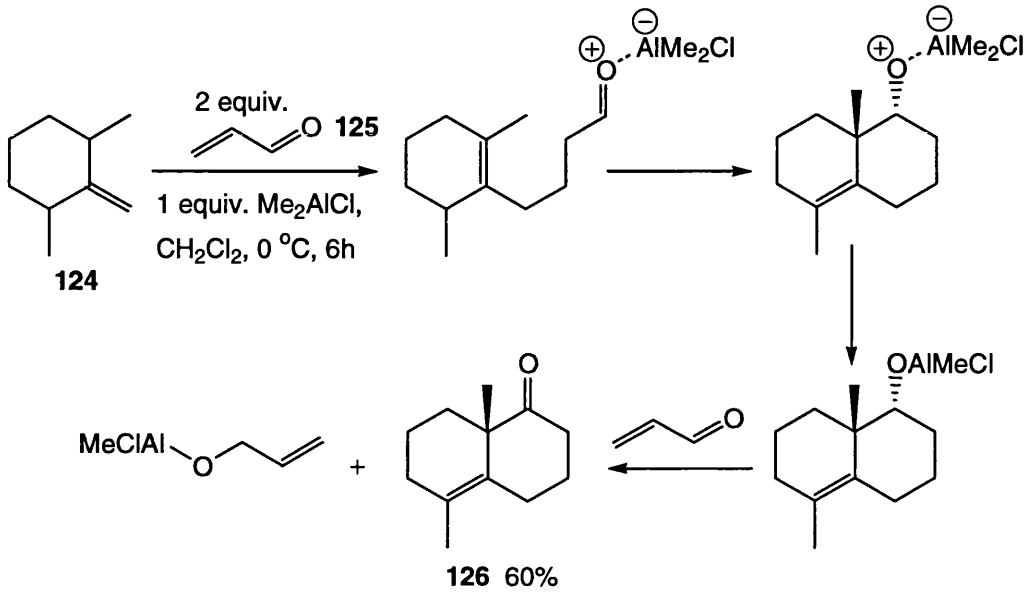


Scheme 61 Synthesis of testosterone through an *in situ* Oppenauer oxidation

However, somewhat surprisingly the reduction with diisobutylaluminium hydride led to the desired product (**123**). The selective oxidation of the carbon-17 alkoxide in an acetone/isopropanol solvent mixture (Scheme 61) was subsequently attributed to an *in situ* Oppenauer oxidation.

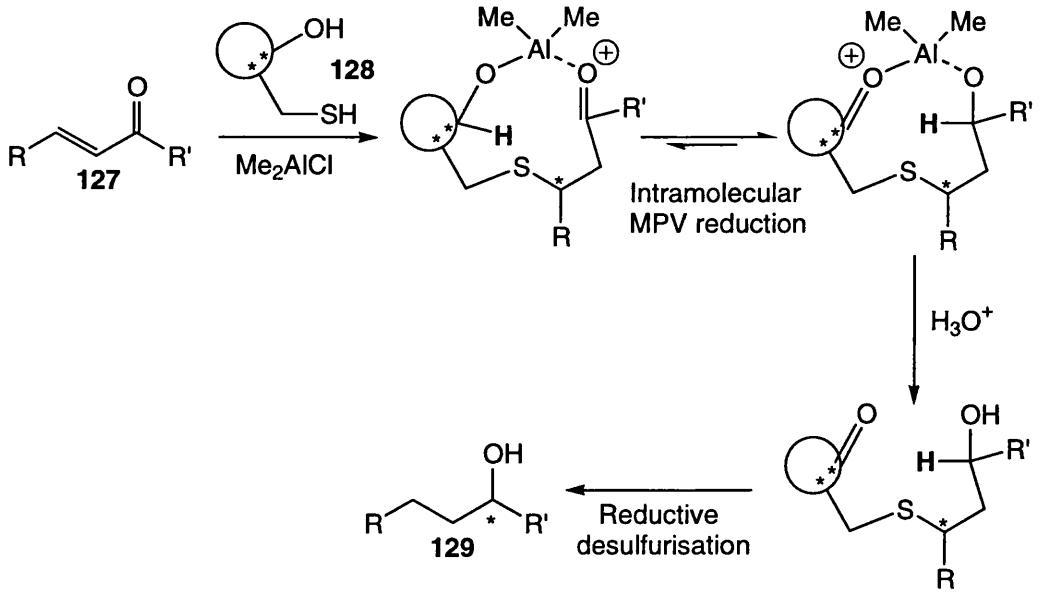
Snider and co-workers were later to report[21] a serendipitous sequential ene-annelation reaction sequence where dimethylaluminium chloride acted as both the ene and Oppenauer catalyst (it is interesting to note that this preceded Nguyen and co-workers' *discovery* of the use of dimethylaluminium chloride as an MPV catalyst[22] by 15 years). Therein, the synthesis of indenone **126** was demonstrated in only two

steps from 2,5-dimethylmethylenecyclopentane **124** when acrolein **125** was utilised as an *in situ* Oppenauer-type oxidant (Scheme 62).



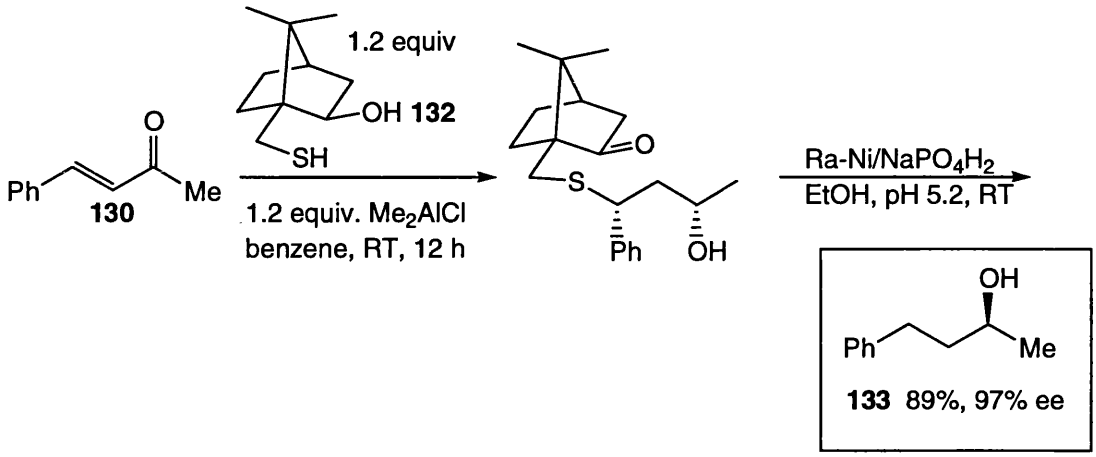
Scheme 62 Domino ene-Oppenauer synthesis of indenone

Recently, Node *et al.*[23,24] have demonstrated that dimethylaluminium chloride is able to catalyse the domino MPV reaction. Therein, it was proposed that a novel tandem Michael addition/MPV reduction of an αβ-unsaturated ketone (**127**) using an enantiomerically pure 1,3-mercaptoalcohol (**128**) should furnish the enantiomerically enriched saturated alcohol (**129**) (Scheme 63).



Scheme 63 Tandem Michael Addition/MPV reduction

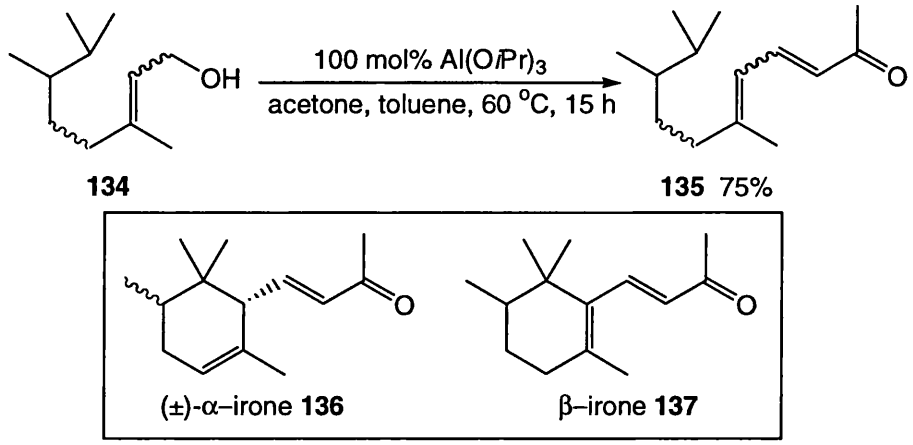
Thus, the reaction conditions were optimised for enone (**130**) and (-)-10-mercaptoisoborneol **132** as the enantiomerically pure alcohol, to provide (*S*)-4-phenyl-2-butanol **133** in 89% yield and 97% ee within 12 hours (Scheme 64).



Scheme 64 Tandem Michael Addition/MPV reduction of benzalacetone

Further work within the paper illustrates the applicability of this technique to the highly enantioselective reduction of acyclic α,β-unsaturated ketones to saturated secondary alcohols or to their benzoates (96-98% ee) and to allylic alcohols (91-98% ee).

In work towards the synthesis of the (±)-α- and β-irones (**136** and **137**), Snowden *et al.*[25] combined both the Lewis acidity and the Brønsted basicity of aluminium isopropoxide in order to catalyse a tandem Oppenauer oxidation/aldol condensation between allylic alcohol (**134**) and the acetone solvent to provide the ketone product (**135**) in 75% yield (Scheme 65).



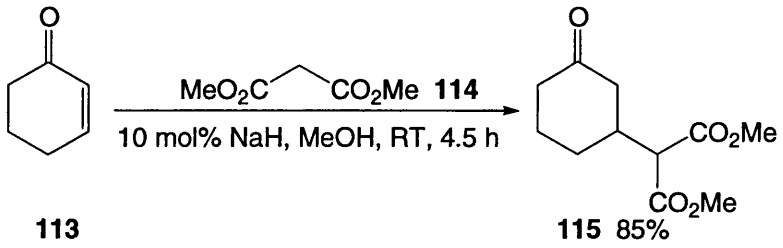
Scheme 65 Tandem Oppenauer/aldol condensation reaction

However, the coupling of a domino Oppenauer oxidation with a Michael addition/MPV reaction i.e. allylic alcohol CEA, would be truly unprecedented and is therefore the study that has been undertaken.

2.2 Preparation of Starting Materials and Control Studies

Initially suitable substrates for the project were chosen. Thus, the Michael acceptor should be both readily available from its alcohol precursor and resistant to obvious side-reactions (for example, direct nucleophilic attack on the carbonyl and aldol condensation reactions). Therefore, 2-cyclohexen-1-one **113**, and its allylic precursor 2-cyclohexen-1-ol **112**, were the proposed starting materials; it was hoped that the formation of a cyclic conjugated product would provide an excellent thermodynamic driving force for the initial oxidation reaction. Furthermore, of the obvious nucleophilic candidates, malonic esters appeared to have significant advantages over the other contenders: general ease of handling counts against both cyanide and cuprate reagents, whereas thiols have a somewhat unpleasant nature. It was therefore decided that the CEA *reaction* between 2-cyclohexen-1-ol **112** and dimethyl malonate **114** would be initially investigated (Scheme 60).

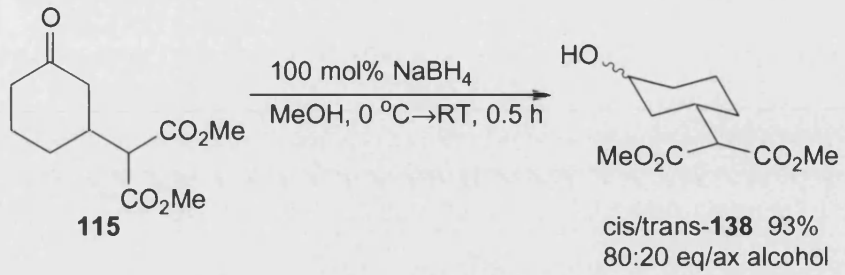
2-(3-Oxo-cyclohexyl)-malonic acid dimethyl ester **115** is not commercially available, however it is easily prepared *via* a simple base-mediated reaction between 2-cyclohexen-1-one **113** and dimethyl malonate **114**, to provide a colourless oil after vacuum distillation[26] (Scheme 66). The structure was confirmed by comparison of the spectroscopic data with literature precedent;[27] the formation of a sharp doublet at 3.36 ppm, assigned to the dimethyl malonate **114** α-proton is a clear indication of product formation.



113 **115** 85%

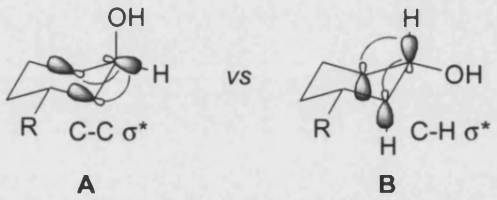
Scheme 66 Formation of 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester

The conversion of ketone (**113**) into the corresponding alcohol, 2-(3-hydroxy-cyclohexyl)-malonic acid dimethyl ester **138** was accomplished using a sodium borohydride reduction to provide a colourless oil in 93% yield after flash column chromatography (Scheme 67).



Scheme 67 Formation of 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester

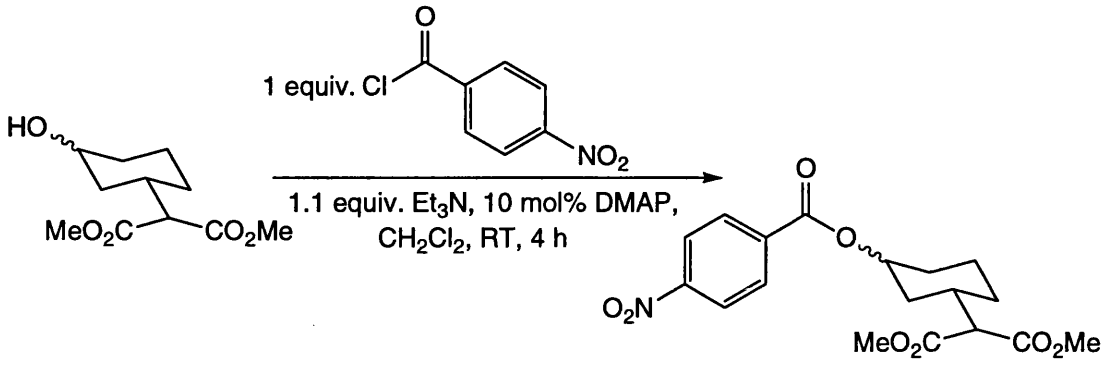
The axial and equatorial isomers were readily distinguished by analysis of the ^{1}H NMR spectrum. Thus the axial and equatorial C**H**-OH proton signals, were observed as a broad singlet at 4.02 ppm and a multiplet at 3.51-3.59 ppm respectively. This separation is attributed to the stereoelectronic effect of the axial and equatorial protons towards the adjacent carbon-hydrogen bond (Scheme 68).



Scheme 68 Influence of stereoelectronic effect on proton chemical shift

Thus, whilst the σ-bond of the equatorial proton interacts with two $\sigma^*_{C\text{-}C}$ orbitals (Scheme 68, **A**), the axial proton interacts with the two adjacent $\sigma^*_{C\text{-}H}$ orbitals (Scheme 68, **B**). Furthermore, a $\sigma^*_{C\text{-}C}$ orbital is a superior electron acceptor to a $\sigma^*_{C\text{-}H}$ orbital, and therefore is able to remove electron density more efficiently. This leads to an increased deshielding effect on the equatorial C-H σ-bond, thus moving the ^{1}H NMR signal to lower field.

The separation of the individual axial and equatorial alcohol products proved to be impossible by flash-column chromatography. Therefore in an attempt to obtain a pure sample of each compound, the alcohol mixture (**138**) was transformed into the *para*-nitro benzoate derivative (**139**) (Scheme 69).

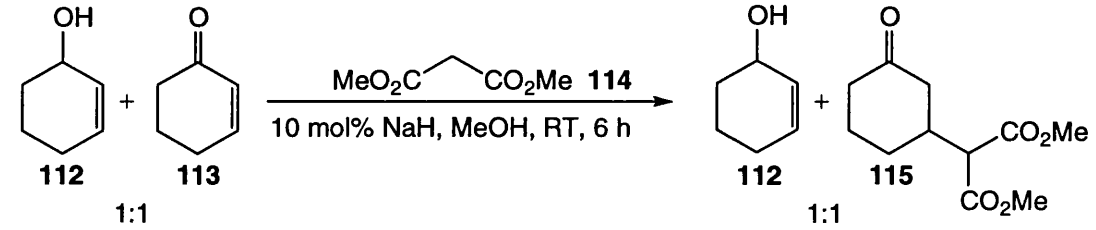


138 cis/trans-**139** 93%

Scheme 69 Derivatisation of alcohol product

However, both the axial and equatorial ester substrates co-eluted by flash-column chromatography and the separation appeared unfeasible. Nevertheless, it was now possible to recrystallise the solid product to provide excellent analytical data.

At this point, it was considered prudent to confirm that 2-cyclohexen-1-ol **112** did not undergo a 1,4-addition with dimethyl malonate **114** and in addition, that it did not hinder the reaction of 2-cyclohexen-1-one **113** with the aforementioned reagent. Thus, a control experiment was subsequently performed in order to confirm that this was the case (Scheme 70).



112 **113** 1:1 **112** **115** 1:1

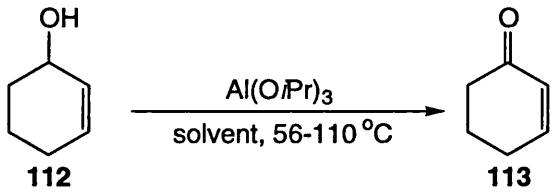
Scheme 70 Michael addition control experiment using 2-cyclohexen-1-ol

The crude product did not display any signals corresponding to the alcohol adduct (**138**) by ^{1}H NMR analysis and, as expected, 2-cyclohexen-1-ol **112** did not significantly hinder the Michael addition towards 2-cyclohexen-1-one **113**.

2.3 Oxidation and Reduction Reactions

Aluminium alkoxides have been used extensively to carry out reversible hydride transfer to a carbonyl acceptor (*vide supra*). The most commonly used reagent, aluminium isopropoxide, is commercially available and effectively promotes both the MPV reduction and Oppenauer oxidation under suitable reaction conditions, generally employing an excess of either reductant (acetone, 2-butanone) or oxidant (isopropanol).

The initial step in the CEA process involves the activation of the allylic alcohol as its enone counterpart. Therefore, the Oppenauer oxidation of 2-cyclohexen-1-ol **112** with aluminium isopropoxide under a variety of conditions was investigated (Scheme 71, Table 1).



112 **113**

Scheme 71 Oppenauer oxidation of 2-cyclohexen-1-ol

Entry	Catalyst [mol%]	Solvent [mL]	*t* [h]	Reductant [mol%]	Conv. [%][a]
1	10	Cyclohexane (5.0)	72	2-Butanone (200)	62
2	25	Acetone (10)	7	-	< 10
3	25	2-Butanone (5)	18	-	44
4	25	Toluene (10)	2.5	2-Butanone (200)	92
5	100	Acetone (10)	18	-	> 95
6	100	Acetone (5)	72	-	> 95
7	100	Toluene (10)	5	2-Butanone (150)	57
8	100	Acetone (10)	24	-	< 5[b]

[a] Analysed by ^{1}H NMR. [b] System contained dimethyl malonate (100 mol%)
Table 1 Results of Oppenauer oxidation of 2-cyclohexen-1-ol

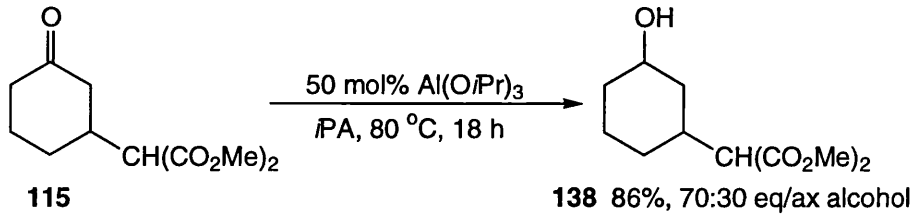
It is known that high boiling point solvents provide good conversions in the Oppenauer oxidation[28] and initial studies focused on the use of a toluene/2-butanone system. Thus under these conditions, an excellent conversion into 2-cyclohexen-1-one **113** within 2.5 hours (Table 1, entry 4) was achieved. However, the relatively

low boiling points of both 2-cyclohexen-1-ol **112** (164-166 °C) and 2-cyclohexen-1-one **113** (168-170 °C) dictated that a cautious removal of toluene *in vacuo* had to be performed in order to provide an accurate measure of conversion by ^{1}H NMR.

A second system was therefore investigated using aluminium isopropoxide and excess acetone as the hydrogen acceptor. Again, an excellent conversion into 2-cyclohexen-1-one **113** was obtained (Table 1, entry 5), although at a higher catalyst loading and with longer reaction times.

In both reaction systems, it was found that the dropwise addition of a solution of aluminium isopropoxide to a solution of substrate at reflux greatly enhanced the conversion. However, somewhat disappointingly, it was demonstrated that performing the reaction in the presence of dimethyl malonate **114** provided a very poor conversion to desired product (Table 1, entry 8). Okano *et al.* have demonstrated[29] that β-diketones deactivate lanthanide (III) catalysts by a strong chelate formation and it is proposed that the dimethyl malonate **114**, a β-diester, is acting in an analogous manner.

Having demonstrated the ability to *activate* 2-cyclohexen-1-ol **112** through the Oppenauer oxidation, the chemoselectivity of the aluminium isopropoxide process was explored by attempting the reduction of ketone intermediate **115** (Scheme 72). This would constitute the final reaction in the domino Oppenauer/Michael addition/MPV reduction process.

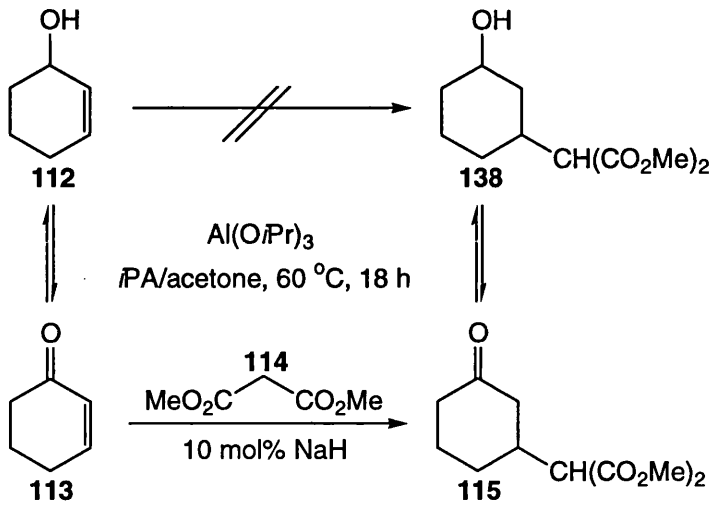


115 **138** 86%, 70:30 eq/ax alcohol

Scheme 72 MPV reduction of Michael addition adduct

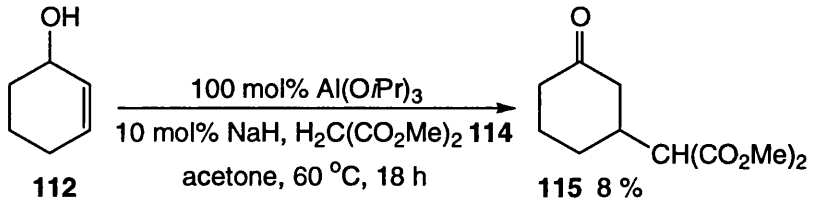
Although a good conversion into alcohol (**138**) was achieved (86%), there appeared to be a minor impurity (~ 10%), which was consistent with an aluminium-catalysed isopropanol transesterification of the methyl ester group.[30,31]

Nevertheless, the project was now at the stage where the following domino reaction scheme could be envisaged (Scheme 73):



Scheme 73 Tandem MPVO-Michael addition reaction

Thus the activation of the allylic alcohol, followed by the *in situ* Michael addition reaction and subsequent hydride transfer from isopropanol would furnish the desired alcohol product. Therefore, the initial *activation*-reaction sequence was investigated and a tandem Oppenauer oxidation-Michael Addition reaction probed (Scheme 74).



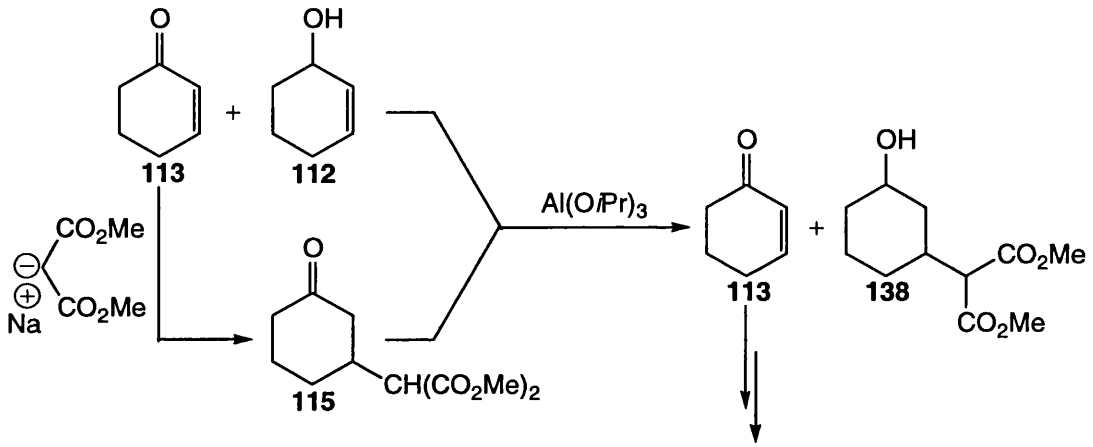
Scheme 74 Tandem MPVO-Michael addition reaction

2-Cyclohexen-1-ol **112** and aluminium isopropoxide were heated to reflux in acetone into which a solution of dimethyl malonate **114** and sodium hydride were added dropwise. However, disappointingly, ^{1}H NMR analysis indicated a very poor conversion into ketone (**115**) (8%). Interestingly both a small amount of unreacted 2-cyclohexen-1-one **113** (10%) and a transesterification product were also observed in the reaction mixture; acetone also displayed a propensity to form aldol-type condensation products (for example mesityl oxide/phorone) under the reaction conditions.

It therefore appeared that an acetone/isopropanol solvent system was incompatible with the substrates and catalyst used, and an alternative procedure had to be sought for the domino Oppenauer/Michael addition/MPV reaction.

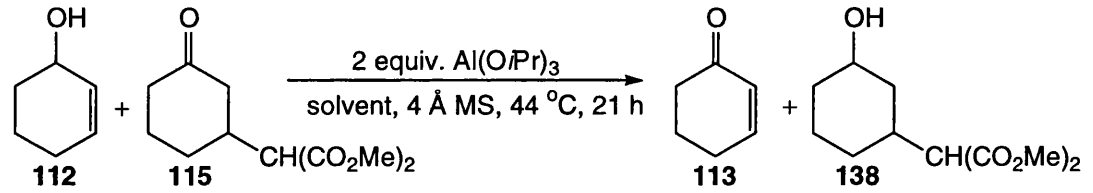
2.4 Catalytic Oppenauer oxidations/ MPV Reductions

It was at this stage of the project that a watershed was reached. In attempting to devise a non-acetone based system, it was realised that if the process were truly catalytic, then there was no requirement for the addition of an external oxidant/reductant i.e. acetone/isopropanol. A catalytic amount of ketone added at the start of the reaction, would as the process turned over, generate more ketone intermediate and therefore more oxidant to restart the cycle (Scheme 75).



Scheme 75 Catalytic domino Oppenauer/Michael Addition/MPV reduction

In order to test this hypothesis a rudimentary crossover experiment was performed whereby a 1:1 mixture of 2-cyclohexen-1-ol **112** and ketone (**115**) was heated to reflux into which a solution of aluminium isopropoxide was added dropwise (Scheme 76).



Scheme 76 Aluminium catalysed Oppenauer/MPV crossover reaction

After 21 hours, ^{1}H NMR analysis indicated that in dichloromethane and in tetrahydrofuran, a 75% conversion into 2-cyclohexen-1-one **113** and alcohol (**138**) was achieved. These data clearly demonstrate that the equilibrium position for the transfer hydrogenation reactions lies firmly to the right, that is towards the thermodynamically more favourable conjugated ketone. This is beneficial for ensuring a constant supply of enone ready for conjugate addition.

After this initial success, the reaction was repeated and a series of solvent systems was evaluated over a reaction time period of six hours (Table 2).

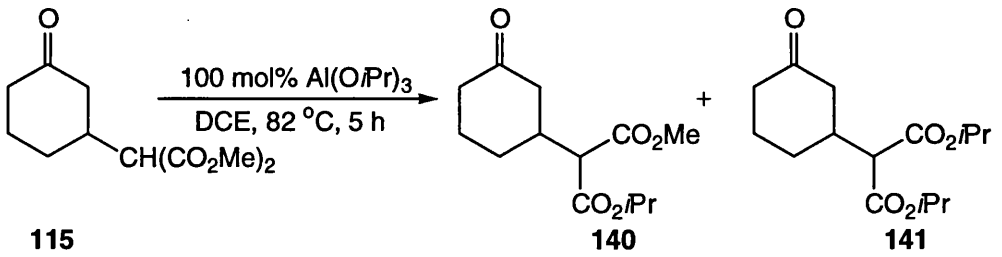
Entry	$Al(OiPr)_3$ [mol %]	Solvent[a]	*t* [h]	Conversion [%][b]	Recovery [%]
1	100	DCE	6	86	100
2	100	THF	6	60	82
3	50	THF	21	66	75
4	100	$CHCl_3$	6	70	85
5	100	Toluene	6	66	76
6	100	Ether	6	50	100
7	100	MeCN	6	75	73
8	100	Hexane	6	63	48
9	100	Cyclohexane	6	75	78
10	100	MeOH	6	5	81
11	100	DMF	6	50	50

[a] The reactions were carried out on a 1 mmol scale in solvent (10 mL) at reflux. [b] Analysed by ^1H NMR.

Table 2 Results of aluminium catalysed Oppenauer/MPV crossover reaction

Whilst the highest conversions were obtained for polar non-coordinating solvents, (Table 2, entries 1, 4, 7 and 9), poorer conversions were obtained for co-ordinating solvents (Table 2, entries 2, 6, 10 and 11). It is possible that these solvents compete with the two substrates for a free site on the catalyst, therefore hindering catalytic activity. Nevertheless, it is difficult to rationalise mechanistically why cyclohexane should act as an efficient solvent. Historically it has been demonstrated that conversion increases with increased temperature and therefore the relatively high boiling point for cyclohexane (79-81 °C) does provide a clue to its efficiency. In addition, the catalyst displays excellent solubility in this solvent.

Further analysis of the ^1H NMR data indicated that in all cases, two significant impurities were observed which appeared consistent with transesterification products. Again, in order to elucidate the nature of these compounds a control experiment was performed (Scheme 77).

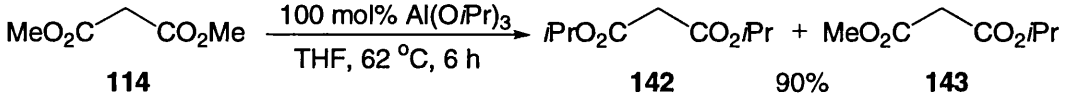


115 **140** **141**

Scheme 77 Aluminium isopropoxide catalysed transesterification of Michael adduct

Thus, ketone (**115**) was heated to reflux in 1,2-dichloroethane into which aluminium isopropoxide was added dropwise and, after 5 hours ^{1}H NMR analysis indicated the formation of two significant products. The major component appeared to correspond to 2-(3-oxo-cyclohexyl)-malonic acid di-*iso*-propyl ester **141**, whilst a second much less significant impurity was difficult to identify, but appeared to be the mono-*iso*-propyl ester product (**140**). This evidence suggests that aluminium isopropoxide is acting as an efficient transesterification reagent,[31] a transformation which was first proposed by Rehberg and co-workers in 1947;[30] the labile methoxy ester groups appear to be easily replaced by the isopropoxide ligands on the aluminium catalyst.

In the light of this evidence, it was therefore considered prudent to investigate the reaction between dimethyl malonate **114** and aluminium isopropoxide. Thus, dimethyl malonate **114** was heated to reflux in tetrahydrofuran followed by the subsequent dropwise addition of aluminium isopropoxide (Scheme 78).



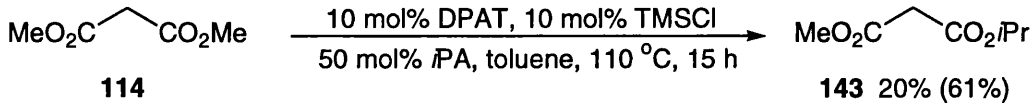
114 **142** 90% **143**

Scheme 78 Aluminium isopropoxide catalysed transesterification of dimethyl malonate

^{1}H NMR analysis of the crude product showed a 90% conversion to the transesterification products malonic acid di-*iso*-propyl ester **142** and *iso*-propylmethylmalonate **143**; the characteristic signal in the ^{1}H NMR (septet, 4.99 ppm) corresponding exactly with the impurity which had been plaguing much of the previous work.

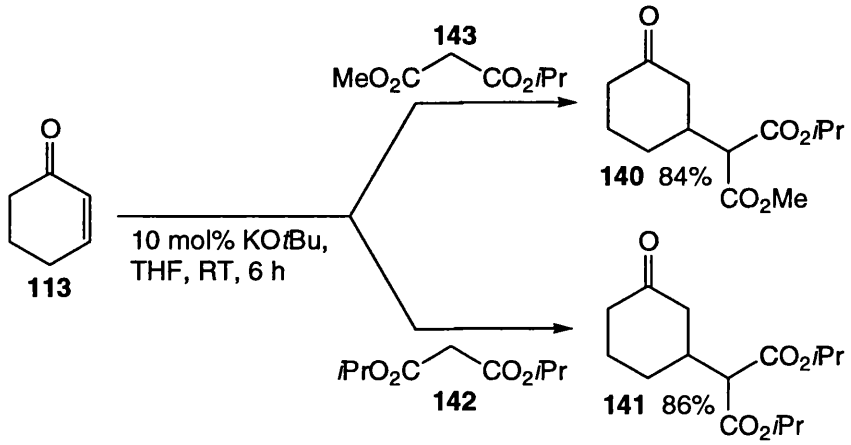
In order to confirm the identities of the transesterification products, an authentic sample of *iso*-propylmethylmalonate **143**, and the corresponding Michael addition adduct (**140**) were prepared.

Diphenylammonium triflate (DPAT) has been demonstrated to be an excellent recent addition to the field of transesterification catalysts.[32] Thus, the DPAT catalysed transesterification between dimethyl malonate and isopropanol smoothly produced the desired mono-isopropyl ester (**143**) in 20% isolated yield (Scheme 79). This represents a 61% theoretical yield.



Scheme 79 DPAT catalysed formation of *iso*-propylmethylmalonate

Both *iso*-propylmethylmalonate **143** and the commercially available di-*iso*-propyl malonate **142** was, subsequently used to prepare the corresponding Michael addition adducts (**140** and **141**) in an analogous manner to that reported for dimethyl malonate (*vide supra*) (Scheme 80). Thus, the analytical data were found to be in agreement with the observed transesterification *impurities*.

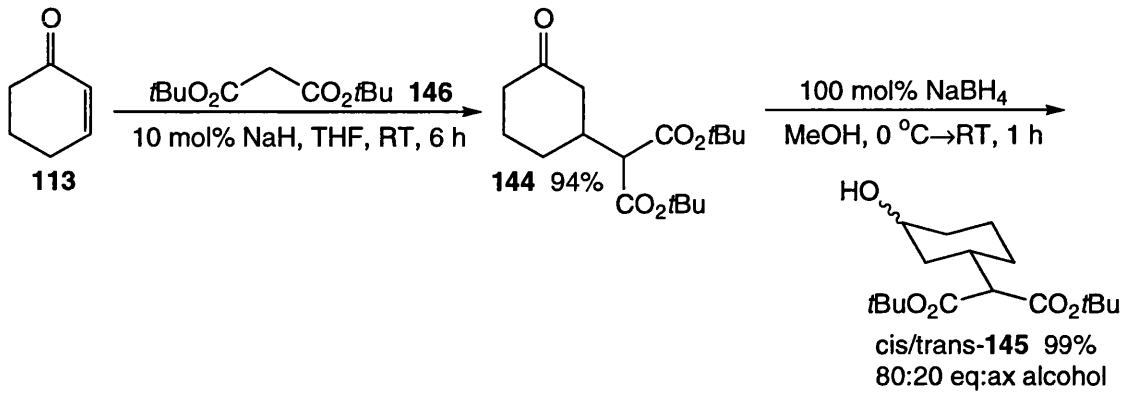


Scheme 80 Formation of mono- and di-*iso*-propyl Michael addition adducts

In the light of this evidence, it was decided that a more robust substrate had to be investigated. In an attempt to block transesterification and base-catalysed hydrolysis reactions, the sterically hindered and base-stable *tert*-butyl ester was chosen; for these substrates transesterification most frequently proceeds through alkyl-oxygen cleavage.[33]

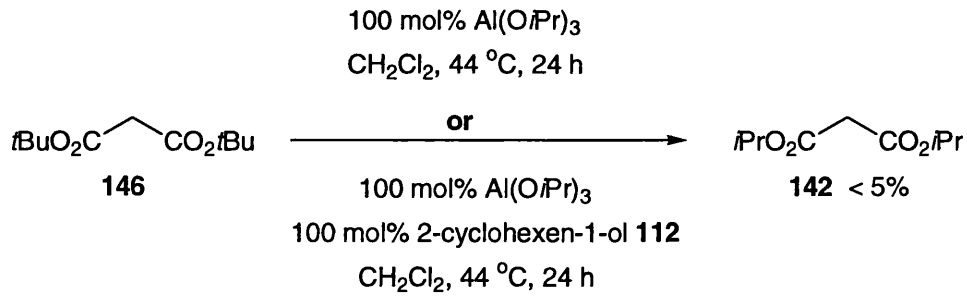
2-(3-Oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester **144** was not commercially available, however it was easily prepared in an analogous manner to ketone (**115**), providing a white crystalline product[34,35] in 94% yield after flash-column

chromatography; the formation ketone (**144**) was confirmed by the presence of a characteristic doublet at 3.08 ppm in the ^{1}H NMR spectra. The ketone (**144**) was subsequently reduced (sodium borohydride) into the corresponding alcohol adduct (**145**) (Scheme 81). The axial and equatorial alcohol isomers were again readily distinguished by analysis of the ^{1}H NMR spectrum. Thus the axial and equatorial C**H**-OH proton signals, were observed at 4.09 and 3.63 ppm respectively.



Scheme 81 Formation of di-*tert*-butyl ester ketone and alcohol adducts

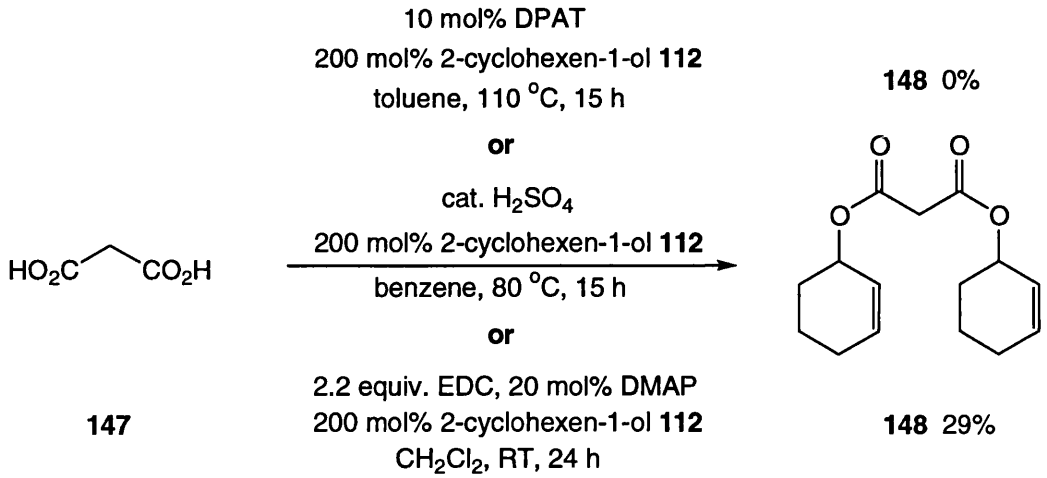
With the knowledge that aluminium isopropoxide was able to transesterify both ketone (**115**) and dimethyl malonate **114** efficiently, it was therefore considered salient to first investigate the corresponding reaction with di-*tert*-butyl malonate **146** (Scheme 82).



Scheme 82 Aluminium isopropoxide transesterification of di-*tert*-butyl malonate

The reaction was performed by adding aluminium isopropoxide dropwise to a dichloromethane solution of starting materials at reflux and, after 24 hours ^{1}H NMR analysis indicated only trace (< 5%) of di-*iso*-propyl malonate **142**. Thus, demonstrating the stability of the *tert*-butyl ester in comparison with the more labile methyl ester. The second control experiment was carried out in order to assess the potential for aluminium catalysed substrate transesterification. However, little evidence for any transesterification products was obtained. Nevertheless, an

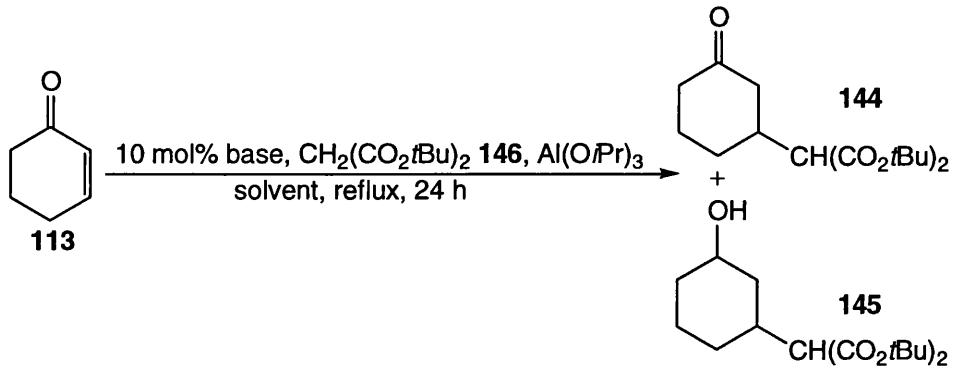
attempted synthesis of 2-cyclohexen-1-ol diester (**148**) was attempted for future comparison (Scheme 83).



Scheme 83 Formation of 2-cyclohexen-1-ol diester from malonic acid

The synthesis of diester (**148**) proved to be somewhat problematic: both a modified DPAT and an acid catalysed transesterification failed (Scheme 83). This was attributed to the possible formation of a stable allylic cation *via* the elimination of water under the reaction conditions. However, the desired product was finally formed in a low yield (29%) using a 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) promoted coupling reaction[36] (Scheme 83).

A second study was proposed in order to determine whether the Michael Addition reaction was perturbed by the presence of the aluminium isopropoxide transfer hydrogenation catalyst. Thus, aluminium isopropoxide was added dropwise to a solution of di-*tert*-butyl malonate **146** and sodium hydride, followed by the addition of 2-cyclohexen-1-one **113** (Scheme 84, Table 3).



Scheme 84 Michael addition reaction in the presence of aluminium isopropoxide

Entry	Base[a] [mol%]	Di-*tert*-butyl malonate [mol%]	Cat. [mol%]	Solvent	Conv. 144:145 [%][b]
1	KO*t*Bu (10)	100	100	THF	< 5:< 5
2	NaH (10)	100	100	CH_2Cl_2	< 5:70
3	NaH (10)	100	10	CH_2Cl_2	71:0
4	NaH (10)	200	10	CH_2Cl_2	100:0
5	NaH (10)	200	100	CH_2Cl_2	<5:>95
6	-	100	100	CH_2Cl_2	0:0

[a] The reactions were carried out on a 1 mmol scale in solvent (10 mL) at reflux for 24 h. [b] Analysed by ^{1}H NMR.

Table 3 Michael addition reaction in the presence of aluminium isopropoxide

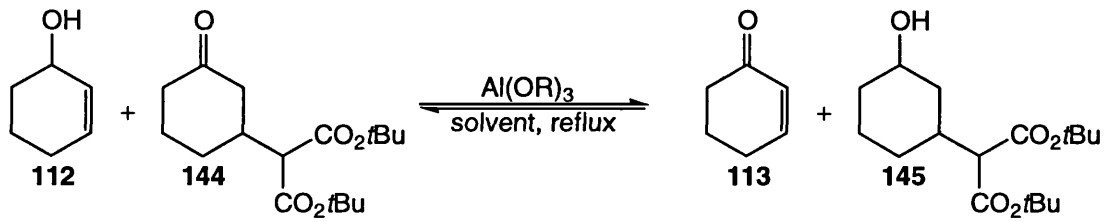
Initially these results appeared somewhat fanciful i.e. the presence of the reduced alcohol product (**145**) (Table 3, entries 2 and 5) in preference to the ketone (**144**) was totally unexpected. However, the alcohol product (**145**) was only obtained under conditions were a stoichiometric amount of aluminium isopropoxide and long reaction times were used (*c.f.* Table 3, entries 3 and 4), and therefore it is reasonable to assume that a hydride transfer between aluminium isopropoxide ligands and ketone (**144**) is occurring *i.e.* the aluminium isopropoxide is acting as a reagent.[37]

Nevertheless, the results do appear to suggest that an excess of di-*tert*-butyl malonate **146** is required in order to achieve a good conversion into ketone (**144**) (Table 3, entries 2-5), however, aluminium isopropoxide was *not* sufficiently Brønsted basic in order to catalyse the reaction in the absence of a formal base (Table 3, entry 6).[38]

2.5 Aluminium *tert*-butoxide catalysed MPVO reactions

Oppenauer's original experiments on sex hormones in the 1930s[39] utilised aluminium *tert*-butoxide as the transfer hydrogenation catalyst. Therein, he demonstrated that excellent yields of ketone products under mild reaction conditions could be obtained. Therefore, it was decided that aluminium *tert*-butoxide should be evaluated in comparison to the results already obtained with aluminium isopropoxide. In addition, the use of aluminium *tert*-butoxide would of course eliminate the possibility of reagent mediated isopropoxide transesterification.

In order to ascertain the equilibrium position for the desired transfer hydrogen reaction, arguably the most important factor in CEA, a 1:1 mixture of 2-cyclohexen-1-ol **112** and ketone (**144**) was heated to reflux in solvent into which aluminium *tert*-butoxide was added dropwise (Scheme 85, Table 4).



112 144 113 145

Scheme 85 Aluminium catalysed Oppenauer/MPV crossover reaction

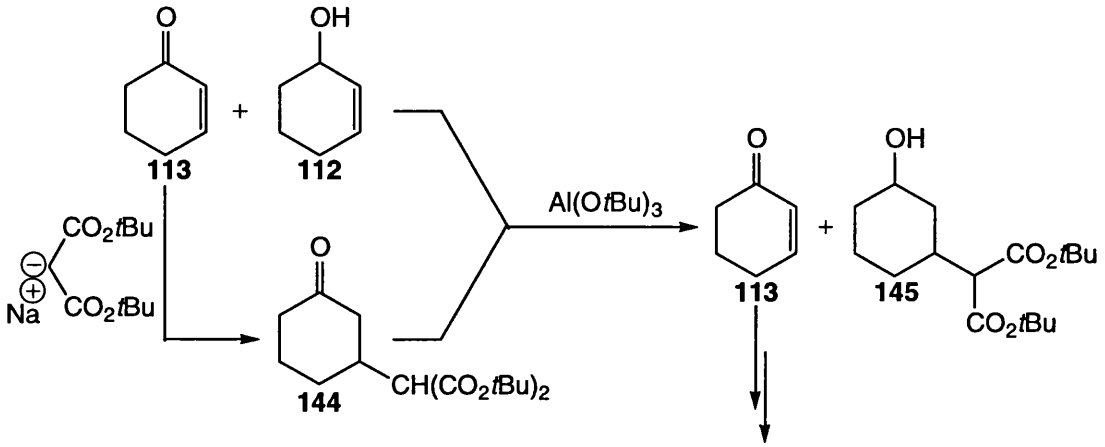
Entry	Catalyst [mol%]	Solvent[a]	*t* [h]	Conversion [%][b]	Recovery [%][c]
1	Al(O*t*Bu)$_3$ (100)	THF	6	> 95	96
2	Al(O*i*Pr)$_3$ (100)	THF	6	< 5	77
3	Al(O*t*Bu)$_3$ (100)	CH_2Cl_2	24[d]	> 95	99
4	Al(O*t*Bu)$_3$ (10)	CH_2Cl_2	24	> 95	100
5	Na(O*i*Pr)$_3$ (100)	CH_2Cl_2	24	< 5	76

[a] The reactions were carried out on a 1 mmol scale in solvent (10 mL) at reflux. [b] Analysed by ^{1}H NMR. [c] Crude recovery upon work-up. [d] Reaction reached completion in 6 hours.
Table 4 Results of Oppenauer/MPV crossover reaction

After 6 hours, ^{1}H NMR analysis of the crude product indicated a > 95% conversion into 2-cyclohexen-1-one **113** and alcohol (**145**) in both tetrahydrofuran and dichloromethane (Table 4, entries 1 and 3), thus proving conclusively that the equilibrium lies towards the thermodynamically more favourable conjugated ketone. Surprisingly, aluminium *tert*-butoxide also exhibited excellent activity at

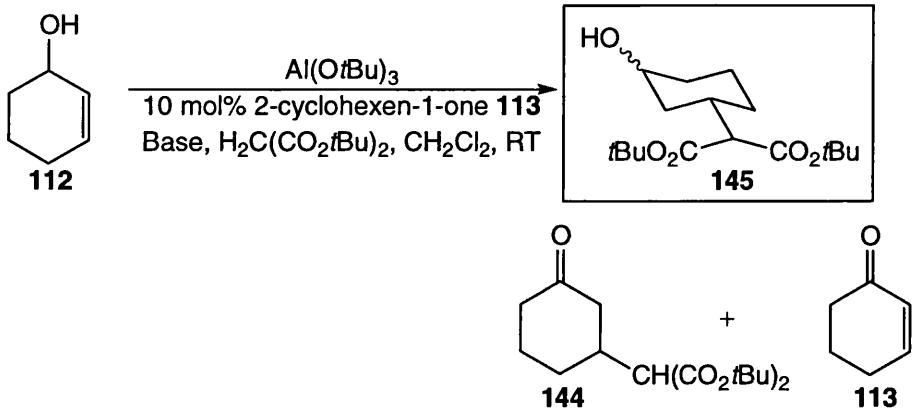
substoichiometric levels (Table 4, entry 4); a property not normally associated with MPV-type systems.[40] However, a repeat experiment conducted at room temperature gave no conversion into the desired products after 6 hours, while the use of a sodium isopropoxide catalyst[41] (Table 4, entry 5) provided equally disappointing results.

The data collected thus far suggested that the following catalytic cycle could be envisaged (Scheme 86):



Scheme 86 Catalytic tandem MPVO- Michael addition reaction

A series of experiments was designed in order to test this hypothesis: the general procedure involved the addition of 2-cyclohexen-1-ol **112** and a catalytic amount of 2-cyclohexen-1-one **113** to a stirred solution of di-*tert*-butyl malonate **146** and sodium hydride in dichloromethane. This solution was subsequently heated at reflux into which aluminium *tert*-butoxide was added slowly over 30 minutes (Scheme 87, Table 5).



Scheme 87 Domino Oppenauer/Michael addition/MPV process

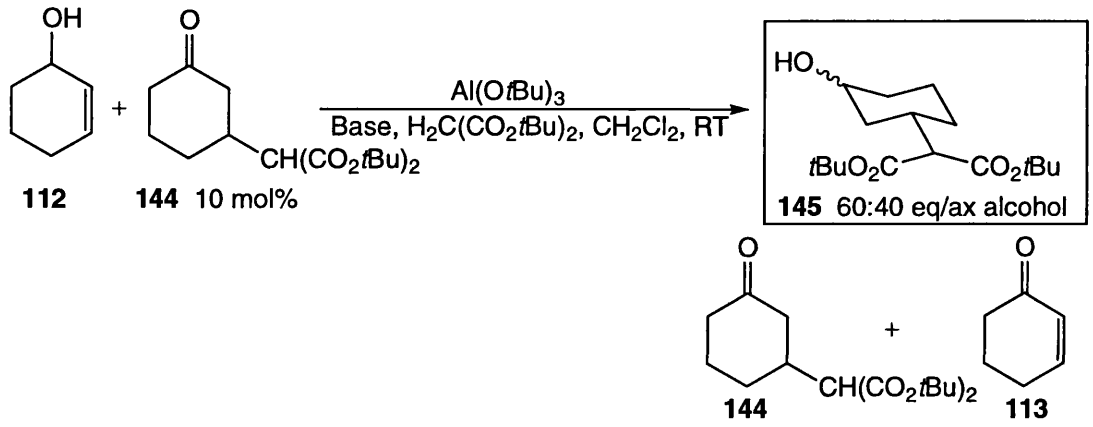
Entry	Base[a] [mol%]	Malonate [mol%]	Al(O*t*Bu)$_3$ [mol%]	*t* [h]	Conv. 145:144:113 [%][b]
1	NaH (20)	200	100	1	12:14:1
2	NaH (20)	200	100	6	19:12:5
3	NaH (10)	200[c]	100	24	0:0:10
4	KO*t*Bu (10)	100[d]	100	24	0:0:10
5	NaH (30)	200	10	24	0:29:0
6	NaH (50)	500	100	24	0:43:0
7	NaH (20)	200	100	72	10:2:6[e]

[a] The reactions were carried out on a 1 mmol scale in CH_2Cl_2 (5-8 mL) at reflux. [b] Analysed by ^{1}H NMR. [c] Added portionwise over 7 hours. [d] Heated at 100 °C in an ACE pressure tube. [e] 5% isolated yield.

Table 5 Results of domino Oppenauer/Michael addition/MPV process

The initial results were rather disappointing: under a variety of experimental conditions, only low conversions (10-19%; Table 5, entries 1,2 and 7) to alcohol (**145**) were obtained, even after 72 hours. Of some concern was the presence of ketone (**144**) in the reaction mixture (Table 5, entries 5 and 6). This suggested that the efficient aluminium catalysed transfer hydrogenation between ketone (**144**) and allylic alcohol (**112**) (Scheme 85) was inhibited by the presence of di-*tert*-butylmalonate **146**.

However, somewhat surprisingly, a repeat experiment using 10 mol% of ketone intermediate (**144**) as reductant provided appreciably enhanced, yet still moderate, conversions to alcohol (**145**) (Scheme 88, Table 6).



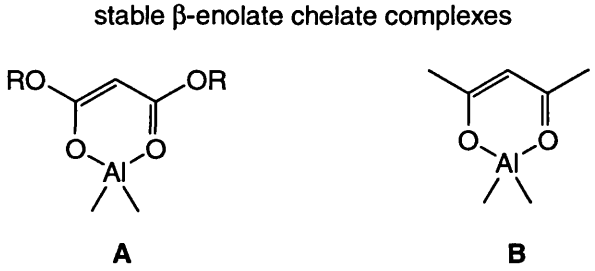
Scheme 88 Domino Oppenauer/Michael addition/MPV process

Entry	Solvent[a] [mL]	Malonate [mol%]	Al(O*t*Bu)$_3$ [mol%]	*t* [h]	Conv. 145:144:113 [%][b]
1	THF (10)	100	100	96	43:20:5
2	THF (10)	100[c]	10	24	29:67:0[d]
3	CH_2Cl_2 (10)	200	100	72	38:0:0
4	CH_2Cl_2 (5)	200	100	10	0:23:0
5	CH_2Cl_2 (5)	200	100	10	10:0:9
6	CH_2Cl_2 (25)[e]	120	100	24	24:0:1

[a] The reactions were carried out on a 1 mmol scale with 10 mol% NaH at reflux. [b] Analysed by ^{1}H NMR. [c] 10 mol% KO*t*Bu. [d] Main product consistent with **148**. [e] 5 mmol in CH_2Cl_2 at reflux.

Table 6 Results of domino Oppenauer/Michael addition/MPV process

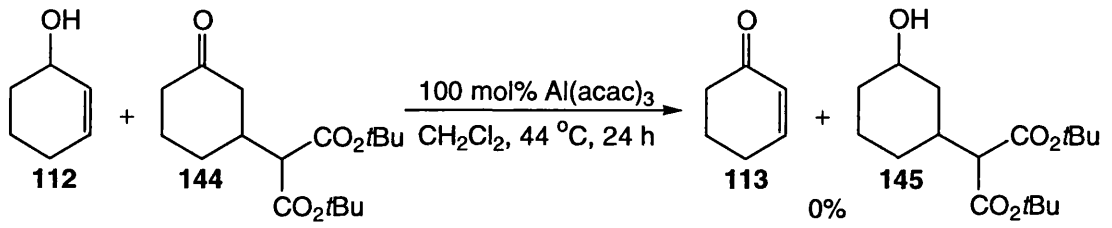
Both Wilds[42] and Okano[29] have reported that β-diketones deactivate aluminium and lanthanide (III) catalysts by strong chelate formation. Furthermore, Okano and co-workers were able to isolate the acetylacetonate complex, Gd(acac)$_3$, which displayed no catalytic activity, from the reaction mixture. It is therefore probable that the low conversions to date are attributed to an analogous complex formation with the malonic ester substrates (Figure 9, **A**).



A **B**

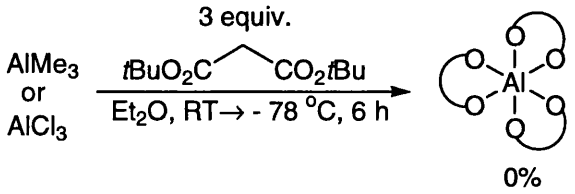
Figure 9 Comparison of proposed aluminium complex and aluminium acetylacetonate

This idea is reinforced by the fact that aluminium acetylacetonate (Figure 9, **B**) was demonstrated to be an ineffective promoter in the Oppenauer/MPV crossover reaction (Scheme 89).



Scheme 89 Aluminium acetylacetonate catalysed Oppenauer/MPV crossover reaction

In order to characterise the proposed aluminium complex, a synthesis of the di-*tert*-butyl malonate aluminium acetylacetonate analogue was attempted. However, syntheses from both trimethyl aluminium and aluminium chloride respectively proved unsuccessful (Scheme 90).

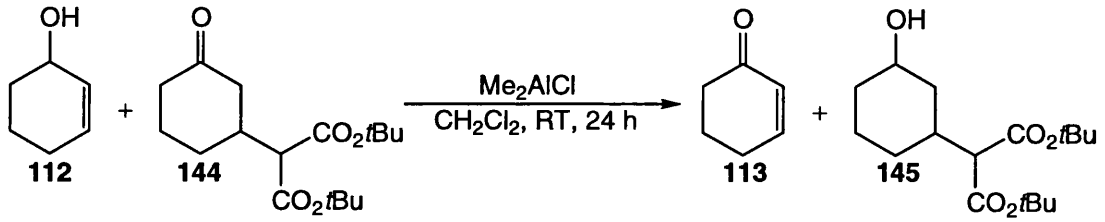


Scheme 90 Formation of tris di-*tert*-butyl malonate aluminium complex

2.6 Dimethylaluminium chloride catalysed MPVO Reactions

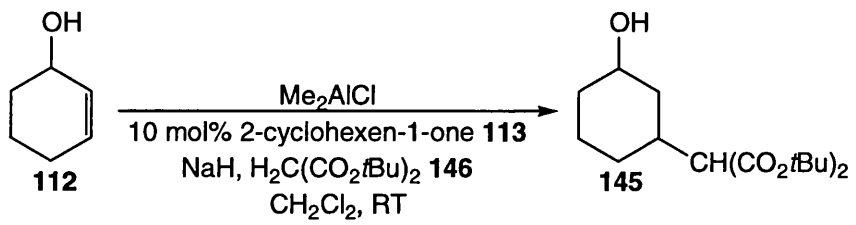
Recent work by Node[23,24] and Snider[21] demonstrated that dimethylaluminium chloride was able to catalyse both a domino Michael addition/MPV reduction and an Oppenauer/ene annelation respectively. In each case, the reaction proceeded at room temperature to give the desired products in excellent yield and, in contrast to aluminium alkoxides, ligand exchange and therefore transesterification is unlikely.

In view of this evidence dimethylaluminium chloride appeared to be an excellent candidate for the domino Oppenauer/Michael addition/MPV process. Thus, the transfer hydrogenation capabilities of dimethylaluminium chloride were investigated for the crossover Oppenauer/MPV process (Scheme 91).



Scheme 91 Dimethylaluminium chloride catalysed Oppenauer/MPV crossover reaction

These promising results prompted further investigation towards the domino Oppenauer/Michael addition/MPV process. The general procedure involved adding dimethylaluminium chloride to a nitrogen purged dichloromethane solution of 2-cyclohexen-1-ol **112**. After 20 minutes, a catalytic amount of 2-cyclohexen-1-one **113**, di-*tert*-butyl malonate **146** and sodium hydride were added and the reaction maintained at room temperature (Scheme 92, Table 7).



Scheme 92 Domino Oppenauer/Michael addition/MPV reaction

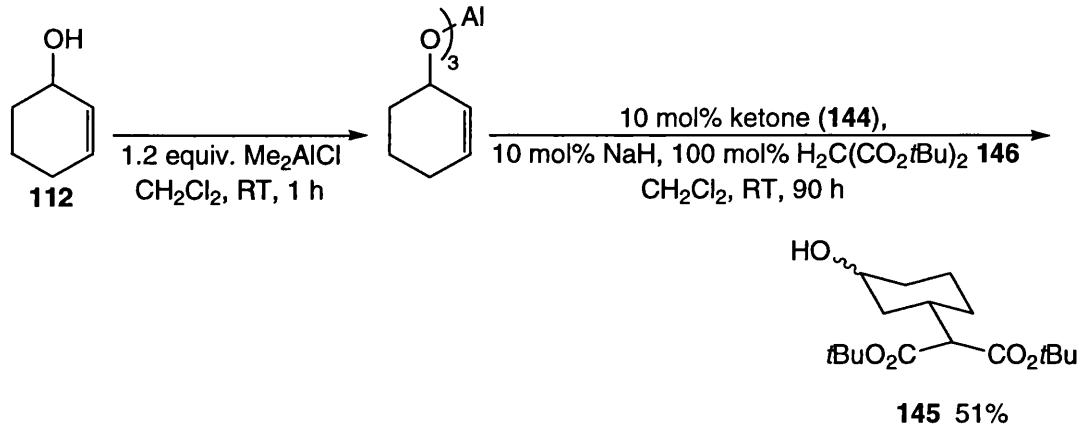
Entry	NaH [mol%]	Malonate[a] [mol%]	Me_2AlCl [mol%]	*t* [h]	Conv. 145:144:113 [%][b]
1	10	100[c]	120	6	9:1:15
2	20	100[c]	120	6	22:12:11
3	10	100[d]	120	24	25:1:5
4	20	100[c]	120	72	11:1:20
5	20	200[c]	120	72	23:12:10

[a] The reactions were carried out on a 1 mmol scale in CH_2Cl_2 (7-10 mL) at room temperature. [b] Analysed by ^1H NMR. [c] 20 mol% 2-cyclohexen-1-one and 4 Å MS were added. [d] 2-Cyclohexen-1-ol and catalyst stirred for 1 hour.

Table 7 Domino Oppenauer/Michael addition/MPV reaction

Unfortunately, the conversions to alcohol (**145**) are still low (9-25%), even after prolonged reaction times (Table 7, entries 4 and 5). However, the presence of unreacted 2-cyclohexen-1-one **113** (Table 7, entries 1-2, 4-5), again suggests that the malonate salt is complexed to the aluminium catalyst, hindering both the Michael addition and MPVO chemistry.

Yager and co-workers[43] demonstrated that the rates of MPVO reactions were directly affected by the degree of pre-association of the aluminium complex and the alcohol substrate. Thus, a final experiment was performed in order to discover whether pre-forming an aluminium tris-cyclohexenyl alkoxide intermediate led to an increase in the rate of reaction (Scheme 94).



Scheme 94 *In situ* generated aluminium alkoxide domino Oppenauer/Michael addition/MPV reaction

Thus, after 90 hours, an increased conversion to alcohol (**145**) (51%) was achieved, however this could only be obtained through the addition of 10 mol% ketone (**144**) at

the start of the reaction. Nevertheless, the formation of the desired product, in moderate conversion and at room temperature was considered a notable achievement.

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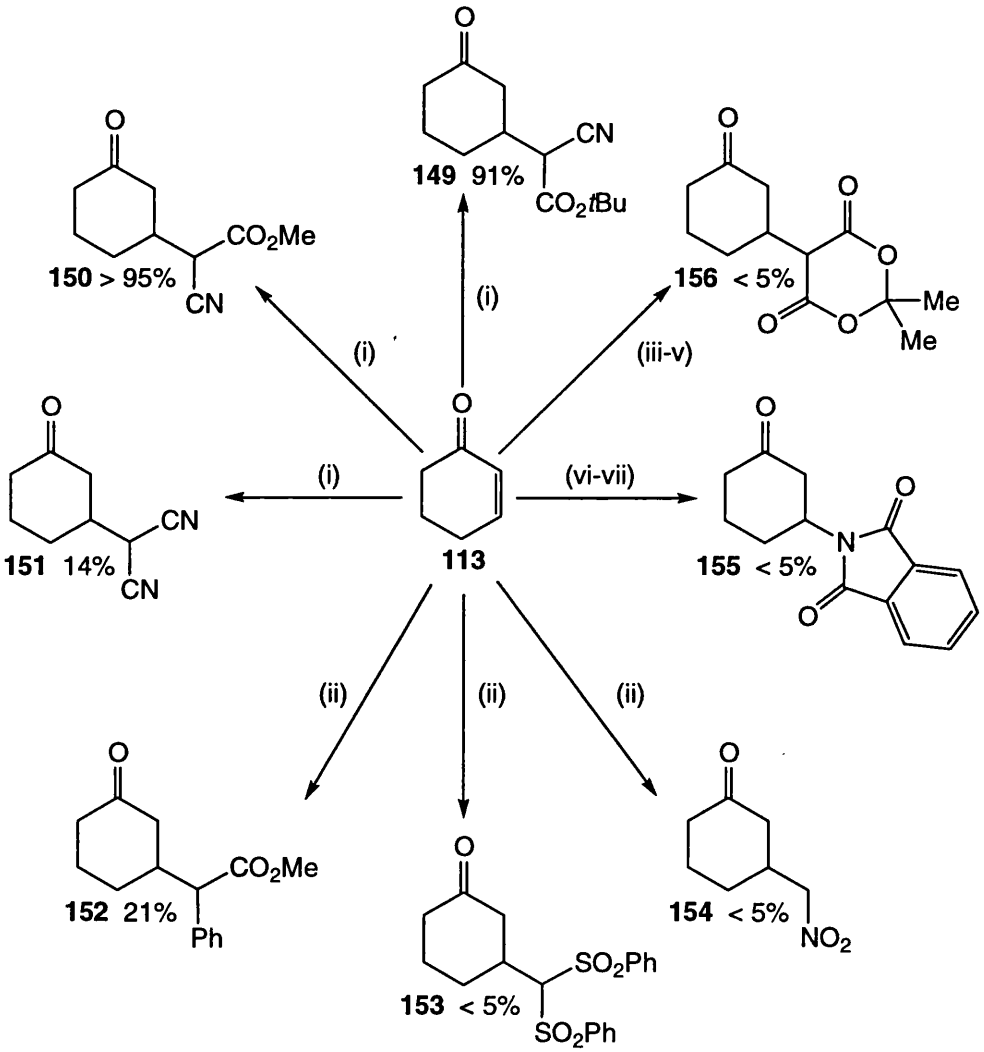
Chapter 3

3.0 Results and Discussion II

3.1 Towards the addition of Methyl Malononitrile to an Allylic Alcohol

In order to realise high conversions in the allylic alcohol CEA procedure it was proposed that alternative nucleophiles should be investigated. Therefore, both symmetrical and unsymmetrical carbon, nitrogen and sulfur nucleophiles were screened for the conjugate addition to 2-cyclohexen-1-one **113** using conditions (i)-(vii) (Scheme 95).

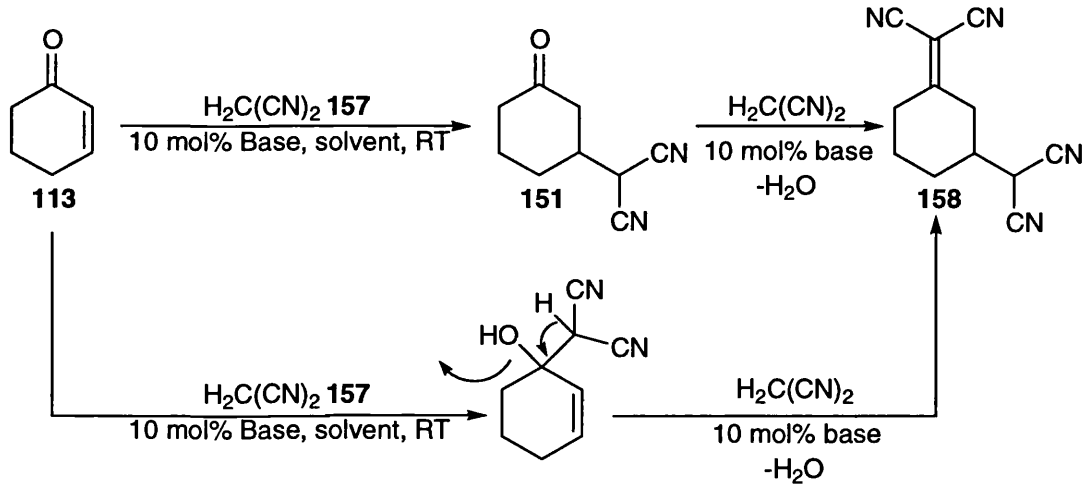


(i) $NCCH_2R$, 10 mol% NaH, THF, RT, 4 h; R = CO_2tBu; CO_2Me; CN
(ii) RCH_2R', 10 mol% NaH, THF, RT, 4 h; R = CO_2Me; H; R' = Ph; NO_2; R = R' = SO_2Ph
(iii) Meldrum's acid, 10 mol% K_2CO_3, THF, 24 h
(iv) Meldrum's acid, 10 mol% NaH, THF, 24 h
(v) Meldrum's acid, 1.25 equiv. 18-crown-6, 10 mol% NaO*t*Bu, THF, 24 h
(vi) Potassium phthalimide, MeOH, RT, 24 h
(vii) Potassium phthalimide, 1.25 equiv. 18-crown-6, DMF, RT, 24 h

Scheme 95 Michael addition screening reactions

However, whilst methyl cyanoacetate, methyl phenyl acetate, and *tert*-butyl cyanoacetate (Scheme 95, **150**, **149**, **152** respectively) were demonstrated to be efficient nucleophiles for conjugate addition, Meldrum's acid, phthalimide, bis-sulfone, nitromethane and malononitrile provided less rewarding results (Scheme 95, **156**, **155**, **153**, **154**, **151** respectively). Nevertheless, in the case of malononitrile **157** a high consumption of starting material *was* observed, but the product did not correspond to a simple Michael addition adduct. Yet, the symmetrical nature and therefore preclusion of diastereomer formation, made malononitrile **157** an appealing substrate.

Malononitrile **157** is a useful building block in synthetic chemistry[1] and it therefore appeared to be an excellent substrate for conjugate addition; a reaction that does have literature precedent.[2] However, after an extensive study (Table 8) it was concluded that this nucleophile presented significant drawbacks (Scheme 96).

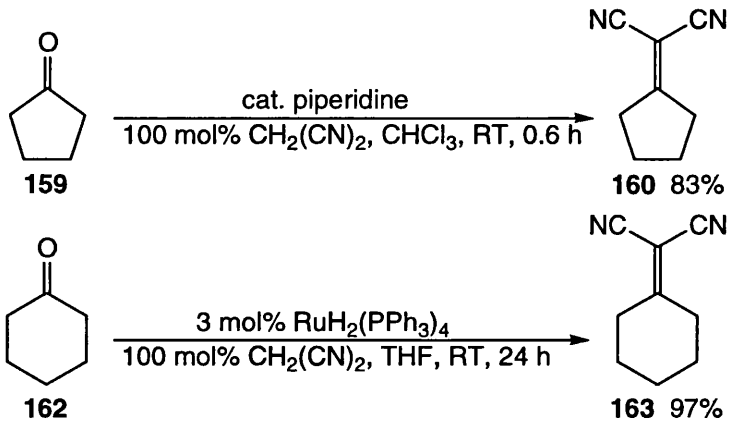


Scheme 96 Addition of malononitrile to 2-cyclohexen-1-one

Entry	Malononitrile [mol%][a]	Base [mol%]	Solvent	*t* [h]	151:158 [%][b]
1	100	NaH (10)	THF	24	14[c]
2	100	$CsCO_3$ (10)	THF	8	15:61
3	100	NaO*t*Bu (10)	THF	1	> 90:0
4	200	NaO*t*Bu (10)	THF	4	43:57
5	100	NaO*t*Bu (10)	THF	8	29:71

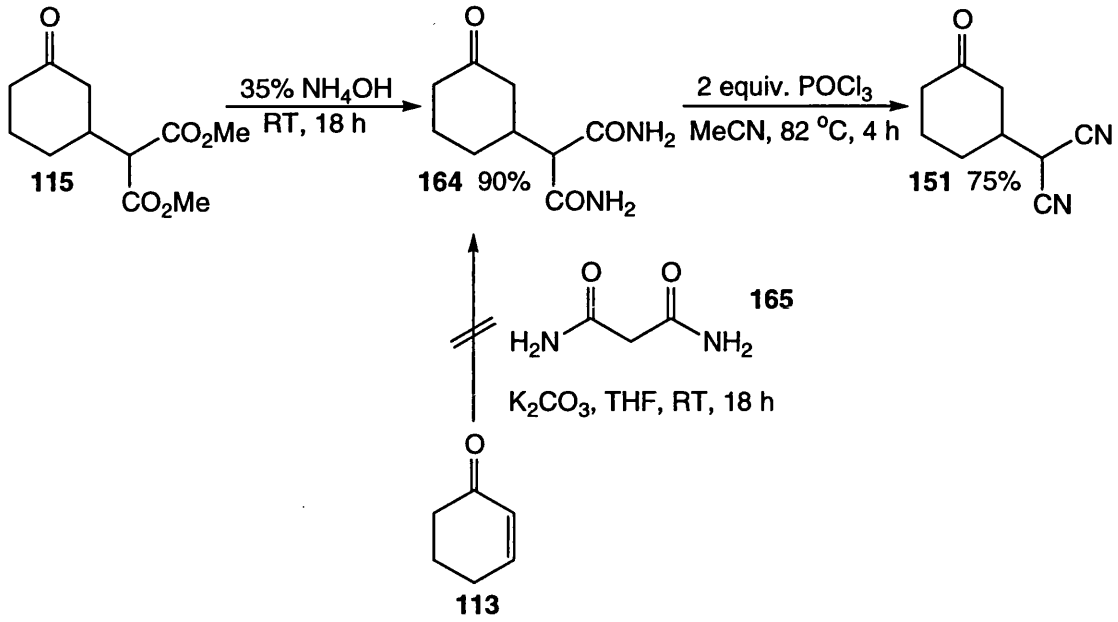
[a] Reactions were performed on a 1 mmol scale in solvent (10-20 mL). [b] Analysed by ^{1}H NMR. [c] Yield of isolated product after column chromatography.
Table 8 Results of the addition of malononitrile to 2-cyclohexen-1-one

Thus, the spectroscopic data, (four nitrile signals in the ^{13}C NMR, 111.5-111.8 ppm) whilst not conclusive, appeared to indicate that a Knoevenagel condensation and subsequent dehydration occurred either preferentially or subsequent to the desired conjugate addition. This is reflected by the observed increase in the conversion into nitrile product (**158**) over time (*c.f.* Table 8, entries 3 and 5). The Knoevenagel condensation of malononitrile **157** to both cyclopentanone **159** and cyclohexanone **162** (Scheme 97) has been reported by Baty and Murahashi respectively[3,4] and is thought to be a consequence of the high acidity of the malononitrile α-carbon (pK_a = 11.2).[5]



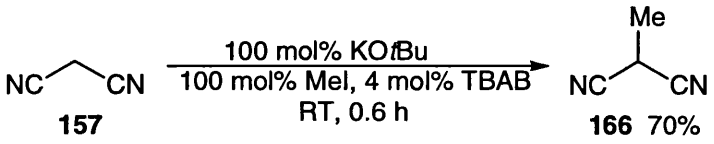
Scheme 97 Knoevenagel condensation of malononitrile with carbonyl compounds

The desired malononitrile Michael addition adduct (**151**) was eventually prepared in a two-step procedure from ketone (**115**). Thus, ketone (**115**) was treated overnight with aqueous ammonia at room temperature, followed by phosphorus oxychloride promoted dehydration to provide 2-(3-oxo-cyclohexyl)-malononitrile **151** in 67% overall yield[6] (Scheme 98). Malonamide (**165**) was, as anticipated, inert to conjugate addition.



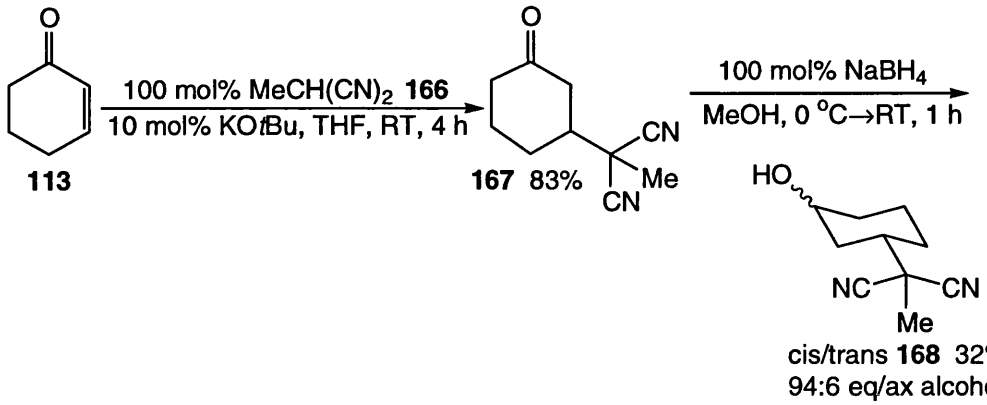
Scheme 98 Synthesis of 2-(3-oxo-cyclohexyl)-malononitrile

It was proposed that a simple solution to prevent the aldol/dehydration reaction was to place a substituent at the α-position of malononitrile **157**. Thus, methylmalononitrile **166** was synthesised according to a recent procedure reported by Díez-Barra and co-workers.[7] This procedure was adopted as other simple base-catalysed routes are known to lead to di-substituted products (Scheme 99).



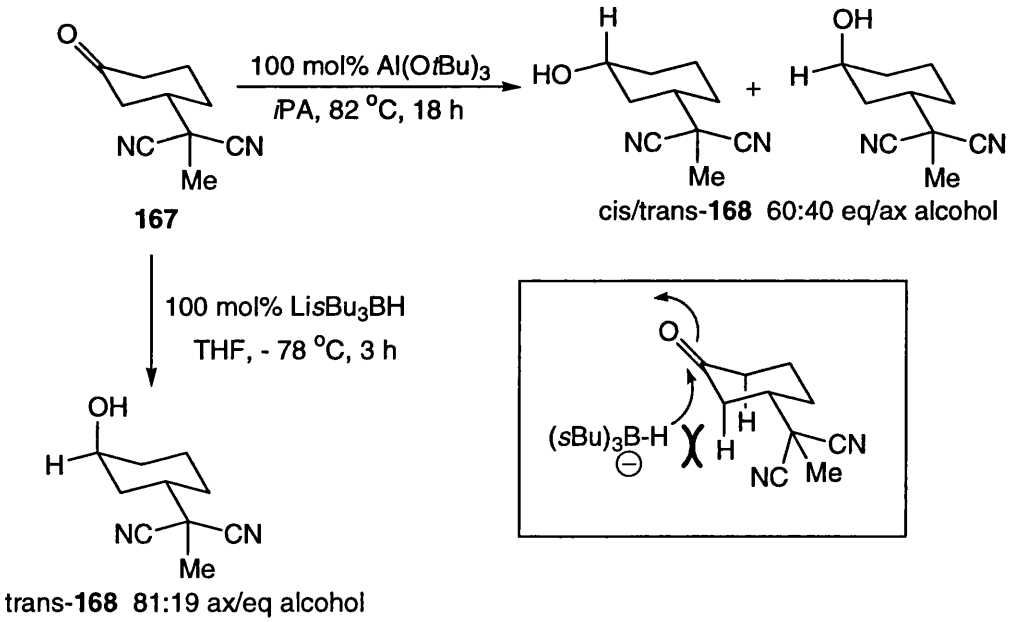
Scheme 99 Synthesis of methylmalononitrile

The nucleophile derived from methylmalononitrile **166** added smoothly to 2-cyclohexen-1-one **113** to provide 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile **167** as a colourless oil in 83% yield. The ketone (**167**) was subsequently reduced (sodium borohydride) into the corresponding alcohol adduct, cis/trans-2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile **168**, as a mixture of cis- and trans-diastereomers (Scheme 100).



Scheme 100 Formation of methylmalononitrile ketone and alcohol adducts

However, in contrast to the ester analogues (*vide supra*), the reduction of ketone (**167**) was somewhat problematic. Whilst, the ketone was smoothly reduced, ^{1}H NMR analysis also indicated that the nitrile groups were susceptible to sodium borohydride reduction over prolonged reaction times (> 1 h).[8-10] In addition, the ratio of diastereomers, was considerably more biased towards the equatorial alcohol; a property that can be attributed to a tendency for approach of the hydride to the carbonyl group in an axial direction (*c.f. tert*-butyl substituted cyclohexanones[11]), leading predominantly to the cis-diastereomer (**168**) (Scheme 100).[12]

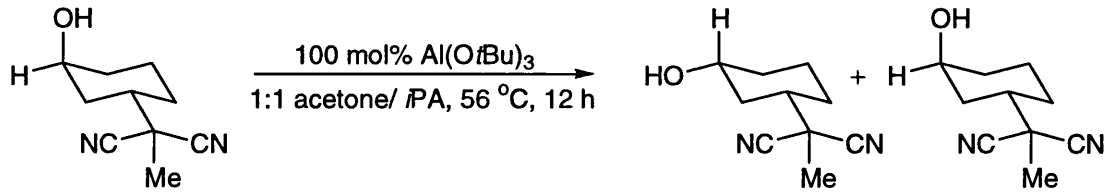


Scheme 101 Comparison of aluminium and boron catalysed ketone reductions

However, somewhat counter-intuitively, the reduction of ketone (**167**) using lithium tri-*sec*-butylborohydride (L-Selectride®),[13] a large highly hindered nucleophile, did not afford the axial alcohol (trans-**168**) exclusively as anticipated.[12] It is therefore

proposed that for ketone (**167**) an axial approach is still a partially favourable route leading to the minor formation of the equatorial alcohol (cis-**168**) (Scheme 101).[12] Conversely, the MPV reduction using aluminium *tert*-butoxide was demonstrated to provide a thermodynamic (equilibrium) product distribution, enabling the isolation of both diastereomers (Scheme 101). In addition, whereas methylmalononitrile adduct (**167**) was again shown to be sensitive to hydride attack[8-10] if the reaction was allowed to reach room temperature, the aluminium catalyst left the nitrile groups untouched.

The thermodynamic product distribution was explored through the equilibration of pure axial alcohol (**168**) in 1:1 acetone/*iso*propanol at reflux (Scheme 102).

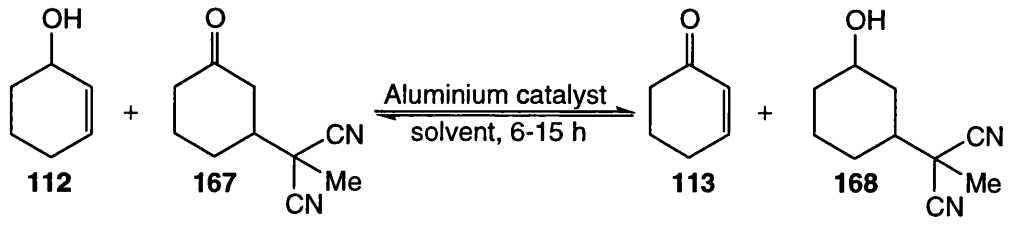


trans-**168** 100% ax cis/trans-**168** 62:38 eq/ax

Scheme 102 Equilibration of axial alcohol

Thus, the axial alcohol (trans-**168**) was efficiently converted into a thermodynamic product ratio (62:38 equatorial/axial) under aluminium *tert*-butoxide catalysis within twelve hours.

The next objective was to establish the equilibrium position for the transfer hydrogenation reaction. Thus, dimethylaluminium chloride and aluminium *tert*-butoxide were investigated for their ability to effect transfer hydrogenation between 2-cyclohexen-1-ol **112** and ketone (**167**) (Scheme 103, Table 9).



112 **167** **113** **168**

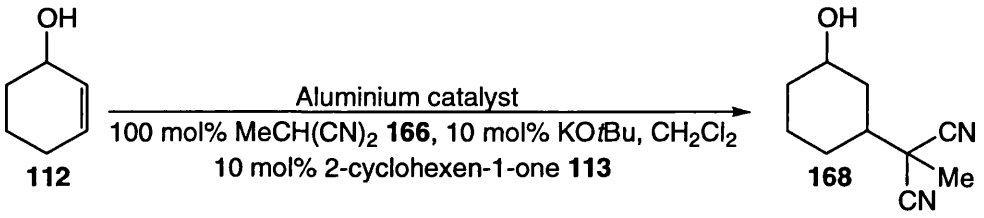
Scheme 103 Aluminium catalysed Oppenauer/MPV crossover reaction

Entry	Catalyst[a] [mol%]	Solvent	Temperature [°C]	*t* [h]	Conversion [%][b]
1	Me_2AlCl (10)	CH_2Cl_2	25	15	> 95
2	Me_2AlCl (10)	THF	25	15	0
3	$Al(OtBu)_3$ (10)	CH_2Cl_2	44	6	> 95

[a] Reactions were performed on a 1 mmol scale in solvent (5 mL). [b] Analysed by ^1H NMR.
Table 9 Results of aluminium catalysed Oppenauer/MPV crossover reaction

These data (Table 9) clearly demonstrate that the equilibrium position for the transfer hydrogenation reaction lies firmly to the right. This is expected due to the formation of the thermodynamically more favourable conjugated ketone. This is beneficial for ensuring a constant supply of enone ready for conjugate addition. However, it was interesting to note that tetrahydrofuran was an appreciably poorer solvent than dichloromethane for the dimethylaluminium chloride catalysed procedure. It is proposed that this is attributable to the co-ordination of the solvent to the catalyst, thus hindering its catalytic activity.

Based on the conditions needed for conjugate addition and for transfer hydrogenation an indirect nucleophilic addition of methylmalononitrile **166** to 2-cyclohexen-1-ol **112** were attempted (Scheme 104, Table 10).



Scheme 104 Aluminium catalysed domino Oppenauer/Michael addition/MPV process

Entry	Catalyst [mol%][a]	CH_2Cl_2 [mL]	Temperature [°C]	*t* [h]	Conversion [%][b]
1	$Al(OtBu)_3$ (100)	10	44	8	69
2	$Al(OtBu)_3$ (100)	8	44	24	> **85**
3	$Al(OtBu)_3$ (100)[c]	10	44	48	**90**[d]
4	$Al(OiPr)_3$ (100)	8	44	24	78
5	Me_2AlCl (100)	5	25	24	43
6	Me_2AlCl (100)[e]	5	25	24	45[d]
7	Me_2AlCl (100)[e]	5	25	24	46
8	Me_2AlCl (100)[e]	5	25	24	45

[a] Reactions were performed on a 1 mmol scale. [b] Analysed by ^1H NMR. [c] Reaction carried out on a 5 mmol scale. [d] Yield of isolated product after flash-column chromatography. [e] Tetrabutylammonium bromide (2/4/10 mol%) added.
Table 10 Results of domino Oppenauer/Michael addition/MPV process

Thus, it was demonstrated for the first time that the domino Oppenauer/Michael addition/MPV process was feasible using methylmalononitrile **166** and aluminium *tert*-butoxide (Table 10, entry 3); it is worth noting that the maximum expected yield is 90%. Significantly poorer yields were obtained when using the dimethylaluminium chloride catalyst (Table 10, entries 5-8), however in principle this could be improved through using a phase-transfer catalyst to increase the dissolution of methylmalononitrile salt in dichloromethane.

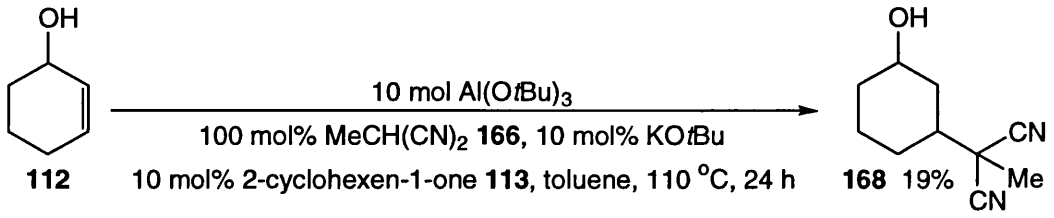
Nevertheless, it was hoped that a fully catalytic reaction could be employed. Thus, both aluminium *tert*-butoxide and dimethylaluminium chloride were investigated for their ability to effect a catalytic domino CEA process (Table 11).

Entry	Catalyst[a] [mol%]	CH_2Cl_2 [mL]	Temperature [°C]	*t* [h]	Yield [%][b]
1	Me_2AlCl (10)	10	25	24	< 5
2	Me_2AlCl (30)	5	25	24	37
3	$Al(OtBu)_3$ (10)[c]	5	44	24	< 5
4	$Al(OtBu)_3$ (10)[c]	3	100	8	**90**
5	$Al(OtBu)_3$ (10)[d]	3	100	8	57
6	$Al(OtBu)_3$ (10)[d]	3	100	8	70

[a] Reactions were performed on a 1 mmol scale. [b] Yield of isolated product after flash column chromatography. [c] Reactions were performed on a 1 mmol scale in an ACE Pressure tube [d] Cyclohexanone (5/10 mol%) used as oxidant.
Table 11 Results of catalytic domino Oppenauer/Michael addition/MPV process

However, poor results were initially obtained when using substoichiometric amounts of catalyst (Table 11, entries 1-3). To address these problems the reactions were studied at elevated temperatures using ACE pressure tubes (Table 11, entries 4-6). Therefore it was extremely rewarding to realise the fully catalytic reaction within eight hours when higher temperatures were employed; even when using 5-10 mol% of cyclohexanone as an alternative catalytic oxidant (Table 11, entries 5 and 6).

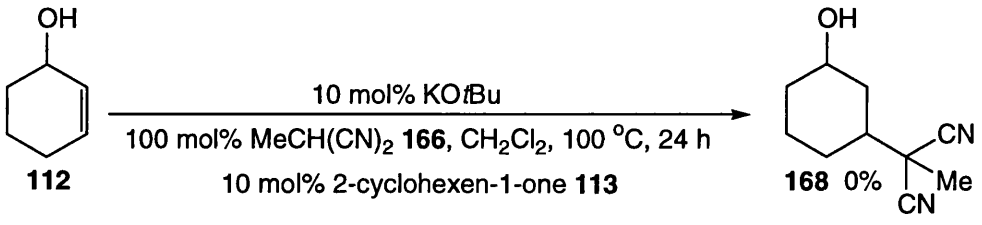
Although an excellent conversion into alcohol (**168**) had been achieved using a catalytic amount of aluminium, it was of some concern that this necessitated the use of elevated temperatures in ACE pressure tubes. It was therefore hoped that the use of toluene as solvent would provide a less cumbersome alternative (Scheme 105) and a method more amenable to process chemistry.



Scheme 105 Aluminium catalysed domino Oppenauer/Michael addition/MPV process

However, toluene was demonstrated to be an inferior solvent to dichloromethane for the allylic alcohol CEA process; this was attributed to poor nucleophile solubility.

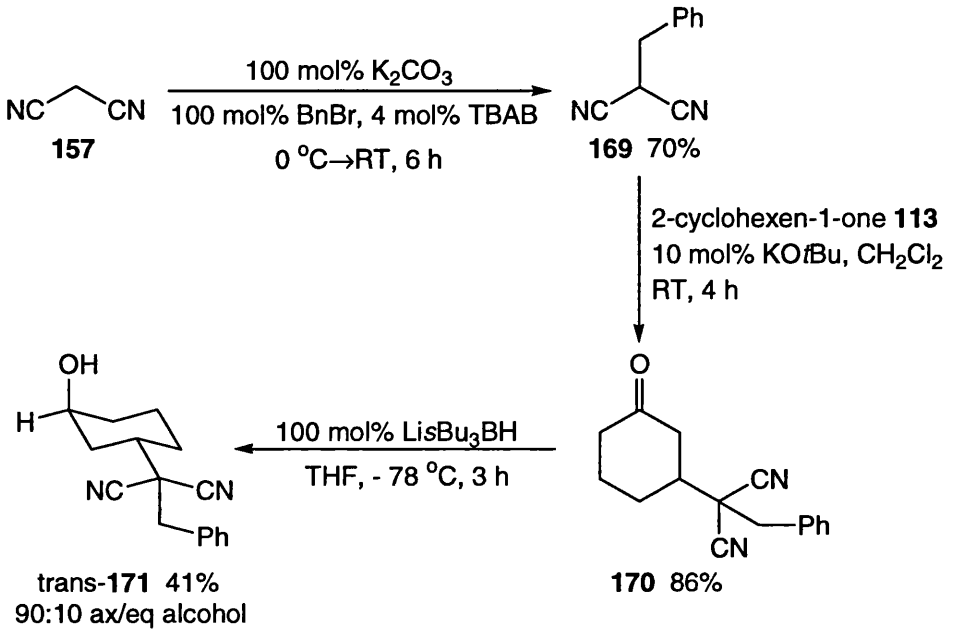
Woodward reported in 1945 that potassium *tert*-butoxide was able to act as a stoichiometric MPV reagent.[14] Therefore it was considered prudent to investigate whether the domino CEA process was in fact catalysed by the base and not the aluminium reagent (Scheme 106).



Scheme 106 Base catalysed domino Oppenauer/Michael addition/MPV process

However, this control reaction clearly illustrates that the presence of the aluminium catalyst *is* essential for the reaction to proceed.

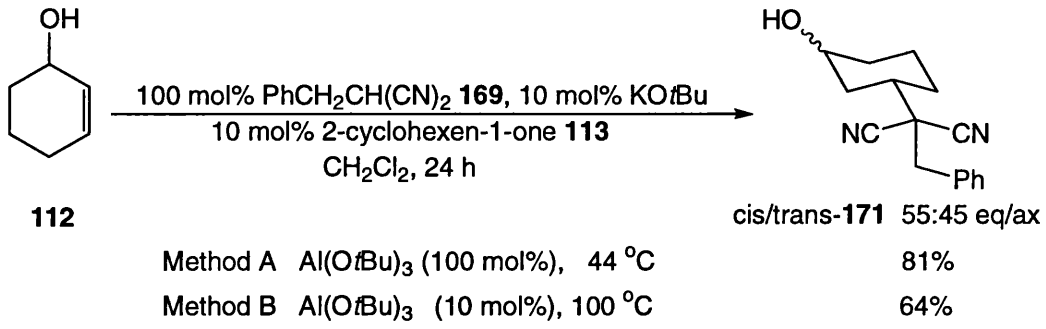
Benzylmalononitrile **169**[7] and the corresponding Michael addition adduct (**170**) were synthesised in an analogous manner to the methylmalononitrile derivatives (Scheme 107).



Scheme 107 Synthesis of benzylmalononitrile derivatives

2-Benzyl-2-(3-hydroxy-cyclohexyl)-malononitrile **171** was subsequently prepared through an L-Selectride® catalysed reduction of ketone (**170**) (Scheme 107) to provide essentially pure axial alcohol, however the poor yield obtained appeared to originate from a sluggish reduction of the nitrile groups.[8-10]

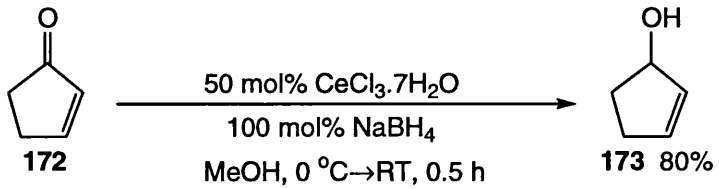
Benzylmalononitrile **169** proved to be an efficient nucleophile in the domino Oppenauer/Michael addition/MPV process. Thus, both the stoichiometric and catalytic reactions proceeded in moderate to good yield (Scheme 108).



Scheme 108 Benzylmalononitrile domino Oppenauer/Michael addition/MPV process

3.2 Cyclopentyl domino Oppenauer/Michael addition/MPV process

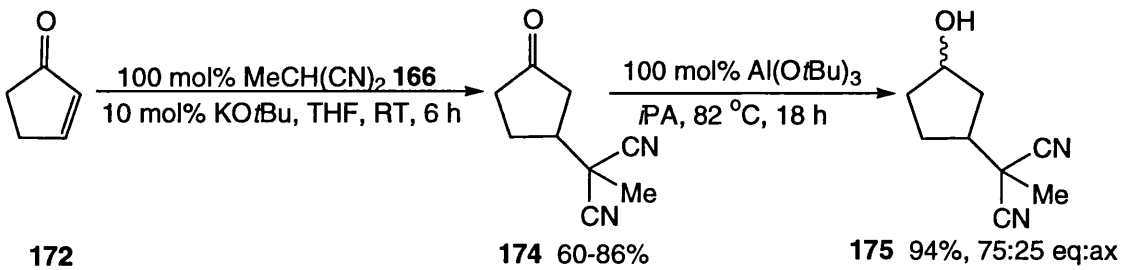
The obvious next step was to expand this procedure towards a cyclopentyl system, however 2-cyclopenten-1-ol **173** was not commercially available, but was easily prepared as a colourless oil after distillation from 2-cyclohexen-1-one **172** using a facile Luche reduction[15] (Scheme 109).



Scheme 109 Synthesis of 2-cyclopenten-1-ol

After some investigation, it was further demonstrated that the stoichiometry of the cerium reagent *was* important. Whilst literature precedent describes the use of both one[15] or more equivalents[16] of cerium chloride, the optimum yield was found to occur under substoichiometric conditions.[17] The use of excess cerium reagent appeared to lead to formation of a biphasic cerium-methanol gel which hindered the recovery of the crude 2-cyclopenten-1-ol **173**.

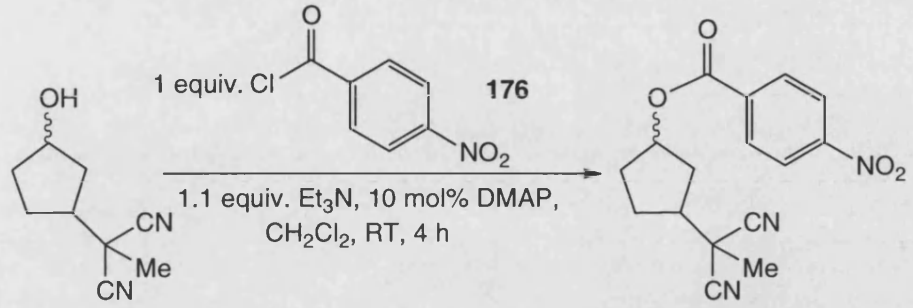
However, the synthesis of 2-methyl-2-(3-oxo-cyclopentyl)-malononitrile **174** did not proceed as efficiently as for the cyclohexyl adducts (*vide supra*). The yield was both irreproducible and necessitated a longer reaction time. An MPV reduction of ketone (**174**) subsequently produced the diastereomeric alcohol derivatives (**175**) as white solids (Scheme 110); an L-Selectride® mediated reduction of ketone (**174**) produced a complicated mixture corresponding to both aldehyde and nitrile products.[8-10]



Scheme 110 Synthesis of methylmalononitrile cyclopentyl adducts

The ^1H NMR data for the assumed axial and equatorial alcohol adducts (cis/trans-**175**) were not as conclusive as for the cyclohexyl derivatives and therefore in an

attempt to obtain samples for X-ray crystallography, the alcohol mixture (±-**175**) was transformed into the corresponding *para*-nitrobenzoate acid **176** derivative (±)-**177** (Scheme 111).



Scheme 111 Derivitisation of alcohol product

Thus, the crystalline product *para*-nitro-benzoic acid 3-(dicyano-methyl-methyl)-cyclopentyl ester cis/trans-**177** was obtained in an excellent yield (90%) after purification. Furthermore, the derivitisation allowed the isolation of both cis- and trans- alcohol adducts (cis- and trans-**177**) which were subsequently submitted for X-ray crystallographic analysis (Figure 10, Appendix 4.6).

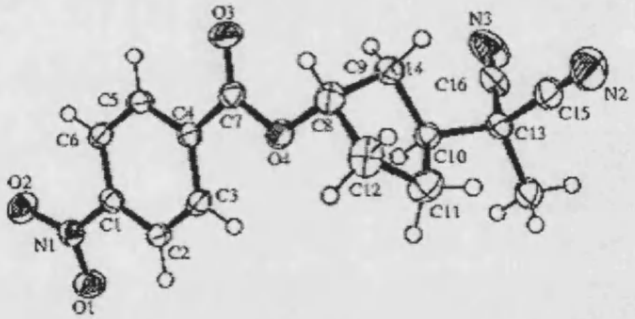
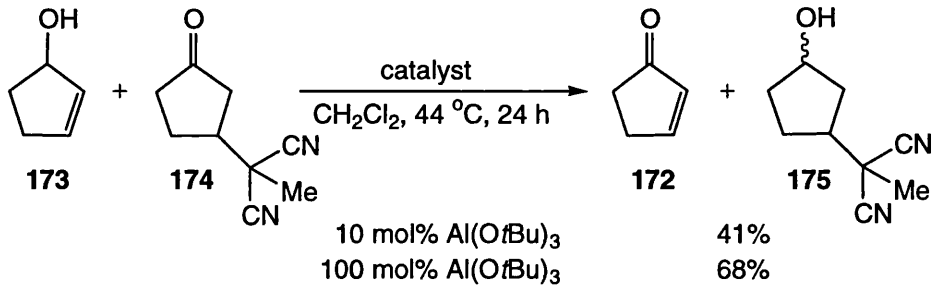


Figure 10 trans-4-nitro-benzoic acid 3-(dicyano-methyl-methyl)-cyclopentyl ester

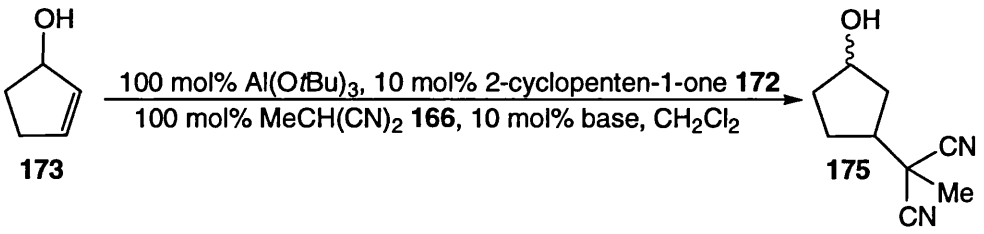
The difference in reactivity between the cyclohexyl and the cyclopentyl methylmalononitrile derivatives was further highlighted by the Oppenauer/MPV crossover reaction (Scheme 112).



Scheme 112 Aluminium catalysed Oppenauer/MPV crossover reaction

Whilst the equilibrium position for the transfer hydrogenation reaction between cyclohexyl derivatives lies firmly to the right (> 90%), the effect is not quite as pronounced for the cyclopentyl adducts. This suggests that the thermodynamic driving force to produce the conjugated ketone is less significant and thus this will have implications for the overall catalytic cycle. A tentative explanation for this data is the steric constraint forced upon the 2-cyclopenten-1-one **172** ring in adopting the required sp^2 bond angles, thus making its formation less favourable. Feringa[18] and Pfaltz[19] have also observed an analogous significant difference in reactivity between 2-cyclohexen-1-one **113** and 2-cyclopenten-1-one **172** towards asymmetric conjugate addition.

As anticipated, the initial results for the attempted domino Oppenauer/Michael addition/MPV process between 2-cyclopenten-1-ol **173** and methylmalononitrile **166** were disappointing (Scheme 113, Table 12)



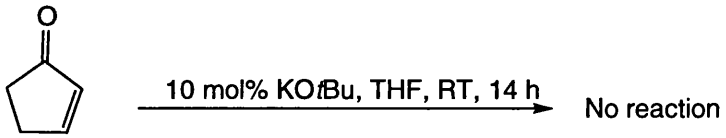
Scheme 113 2-cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process

Entry	Base[a] [mol%]	CH_2Cl_2 [mL]	Temperature [°C]	*t* [h]	Yield [%][b]
1	KO*t*Bu (10)	5	44	6	< 10
2	KO*t*Bu (10)	5	44	24	26
3	KO*t*Bu (10)	5	44	24	27
4	NaO*t*Bu (10)	5	44	24	31
5	KO*t*Bu (10)[c]	3	100	24	**60**
6	KO*t*Bu (10)[c]	3	150	24	61
7	KO*t*Bu (10)[c,d]	5	100	24	51

[a] Reactions were performed on a 1 mmol scale. [b] Yield of isolated product after flash column chromatography. [c] Reactions were performed on a 1 mmol scale in an ACE Pressure tube [d] Reaction performed on a 2 mmol scale in an ACE Pressure tube.

Table 12 Results of 2-cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process

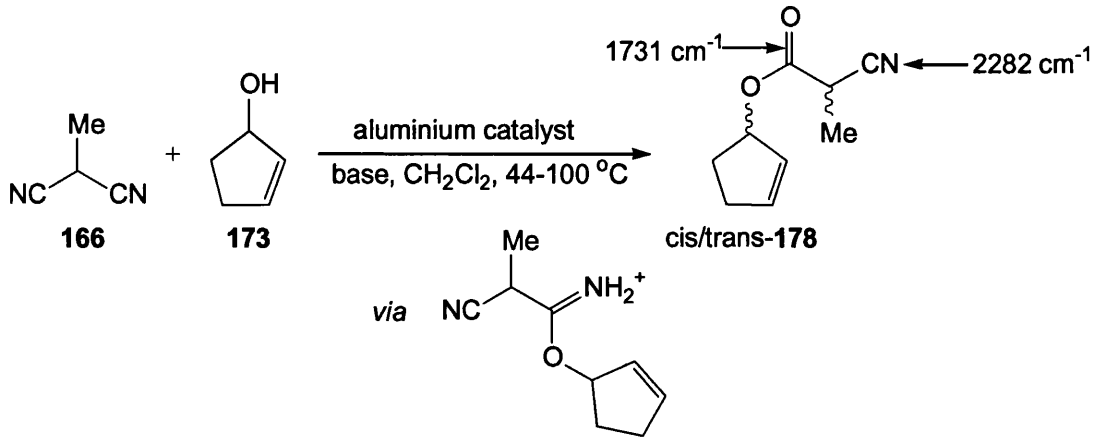
However, although poor (yet reproducible) results were obtained using solvent at reflux (Table 12, entries 1-4), an increase in temperature does provide an appreciable enhancement in yield (Table 12, entries 5-7). Nevertheless, these yields are moderate in comparison with the cyclohexyl system (*vide supra*). It was initially proposed that this could be a consequence of an aldol-type self-condensation of 2-cyclopenten-1-one **172** (Scheme 114),[20] however, both this reaction and a control reaction between methylmalononitrile and base (malononitrile itself can form a dimeric product[1]) did not lead to any significant results.



172 **or** 10 mol% KO*t*Bu, THF, 66 °C, 14 h

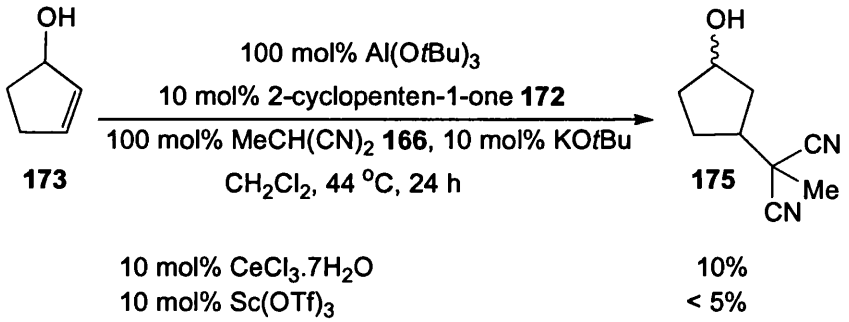
Scheme 114 Control reaction between 2-cyclopenten-1-ol and base

It is therefore suspected that the lower recovered yield for the 2-cyclopenten-1-ol **173** domino Oppenauer/Michael addition/MPV process is attributable to a competing side reaction (e.g. Pinner[21] or Ritter[22] reaction). Although the spectroscopic data were somewhat inconclusive, isolated minor impurities from the 2 mmol scale reaction (Table 12, entry 7) appeared to be consistent with diastereomeric nitrile alcoholysis products cis/trans-**178** (Scheme 115). It is possible that a combination of the increased reactivity and steric bulk of 2-cyclohexen-1-ol **112** precludes an analogous alcoholysis reaction.



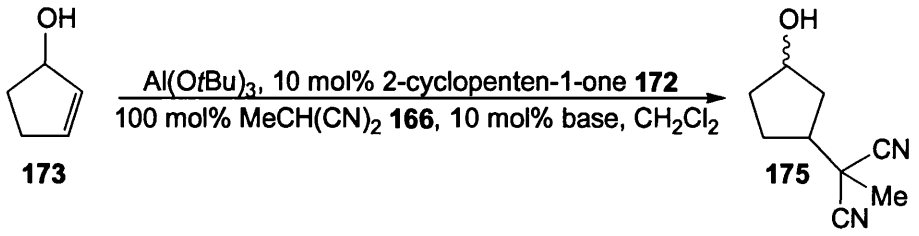
Scheme 115 Suspected nitrile alcoholysis product

It was therefore proposed that further experiments should be conducted using scandium triflate[23,24] and cerium chloride heptahydrate[22] additives in order to activate the 2-cyclopenten-1-one **173** intermediate towards conjugate addition (Scheme 116).



Scheme 116 2-Cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process

However, the Lewis acid additives appeared to retard rather than accelerate the reaction and two further approaches were thus explored: organic (Appendix 2) and fluoride bases (Scheme 117, Table 13).



Scheme 117 2-Cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process

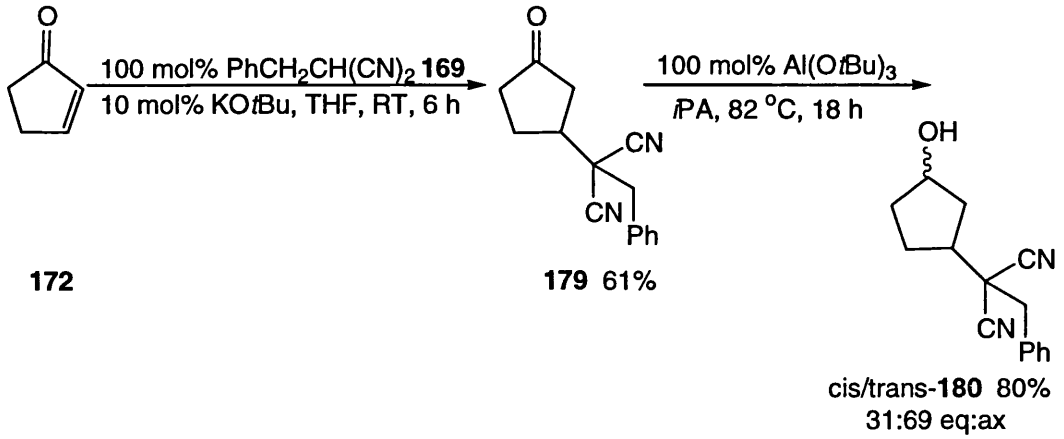
Entry	$Al(OtBu)_3$ [mol%][a]	Base [mol%]	CH_2Cl_2 [mL]	Temp. [°C]	*t* [h]	Conv. [%][b]
1	100	CsF (5)	5	100	24	< 5
2	100	CsF (10)	5	100	20	**71**
3	100	CsF (30)	5	100	24	56
4	10	CsF (100)	5	100	24	< 5
5	100[c]	DBU (10)[d]	5	44	24	< 5
6	100	MTBD (10)[e]	3	100	24	48[f]

[a] Reactions were performed on a 1 mmol scale in an ACE Pressure tube. [b] Analysed by ^1H NMR. [c] Reaction was performed on a 1 mmol scale in solvent at reflux. [d] 1,8-Diazabicyclo[5.4.0]undec-7-ene. [e] 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene. [f] Yield of isolated product after flash column chromatography.

Table 13 Results of 2-Cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process

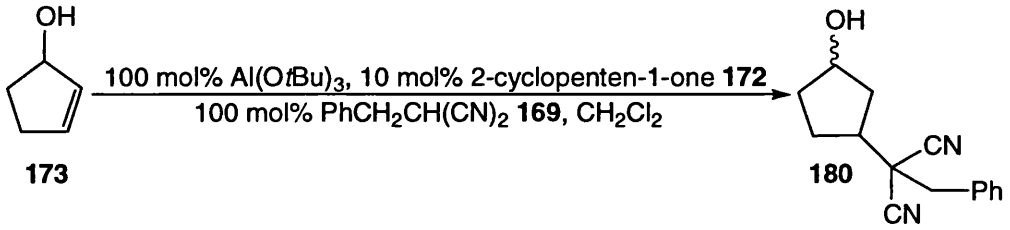
Thus, catalytic caesium fluoride (Table 13, entry 2) was demonstrated to be an excellent base in the domino Oppenauer/Michael addition/MPV process; Michael addition reactions using caesium fluoride do have literature precedent: Yamaguchi and co-workers[25] have previously reported the stereoselective addition of di-*tert*-butyl malonate **146** to 2-cyclohexen-1-one **113** catalysed by 20 mol% of caesium fluoride. In addition, fluoride bases provided a very 'clean' reaction profile, that is the use of fluoride base appeared to suppress the minor side-reactions, which were previously observed. This trend was also reflected in the result obtained using the strong organic base, MTBD (pK_a ~ 23).[26] Whilst the weaker organic base DBU (pK_a 11-12), did not display any activity in the allylic alcohol CEA process (Table 13, entry 6), MTBD *was* able to catalyse the reaction in moderate yield (Table 13, entry 6).

The problems associated with 2-cyclopenten-1-ol **173** were again exhibited with the domino reaction using the nucleophile derived from benzylmalononitrile **169**. In an analogous manner to the formation of ketone (**174**), the yield of 2-benzyl-2-(3-oxo-cyclopentyl)-malononitrile **179** was also moderate (Scheme 118).



Scheme 118 Formation of cyclopentyl benzylmalononitrile derivatives

Nevertheless, the domino Oppenauer/Michael addition/MPV process between 2-cyclopenten-1-ol **173** and benzylmalononitrile **169** was attempted (Scheme 119, Table 14).



Scheme 119 2-Cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process

Entry	KO*t*Bu [mol%][a]	CH_2Cl_2 [mL]	Temp. [°C]	*t* [h]	Conv. [%][b]
1	10	6	44	24	19
2	10	5	85	24	44
3	10	5	100[c]	24	21[d]
4	-	5	100[c]	24	44
5	-	5	100[c]	72	**60**[d]

[a] Reactions were performed on a 1 mmol scale in solvent at reflux. [b] Analysed by ^{1}H NMR. [c] Reactions were performed on a 1 mmol scale in an ACE Pressure tube. [d] Yield of isolated product after flash column chromatography.

Table 14 Results of 2-Cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process

Whilst the yield of alcohol (**180**) was low at both reflux and elevated temperatures (Table 14, entries 1-3), a moderate yield was finally obtained through using a system in which the potassium *tert*-butoxide base was omitted (Table 14, entry 5). It

therefore appeared that under the prolonged high temperatures, the aluminium catalyst was able to form the desired malononitrile nucleophile (Figure 11),[27] whilst not possessing sufficient Brønsted basicity to facilitate nitrile alcoholysis.

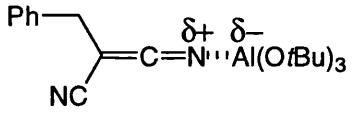


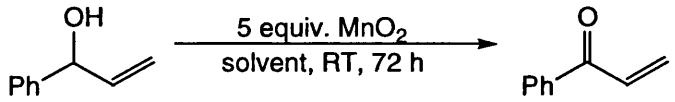
Figure 11 Proposed Benzylmalononitrile aluminium complex

In summary, it has been demonstrated that whilst nucleophiles will not normally add to allylic alcohols, this reaction becomes possible by a procedure involving catalytic electronic activation of the substrate.

3.3 Towards the addition of Methyl Malononitrile to Linear Allylic Alcohols

The next step was to investigate whether the allylic alcohol CEA procedure was applicable to linear substrates. However, an obvious drawback to this methodology was that substitution at the double bond terminus would lead to diastereomeric products; a problem not encountered with symmetrical nucleophiles and cyclic substrates. Therefore for simplicity, it was proposed that the initial investigations should focus on 3-phenyl-1-propen-3-one **183**, an unsubstituted starting material.

3-phenyl-1-propen-3-one **183** was not commercially available, however, the synthesis from the alcohol precursor, α-vinyl benzyl alcohol **182** appeared facile. Thus, α-vinyl benzyl alcohol **182** was subjected to manganese dioxide catalysed oxidation in both ethyl acetate[28] and dichloromethane (Scheme 120).

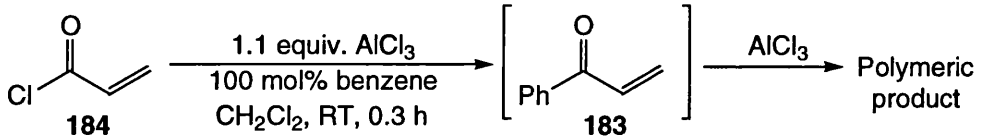


182 **183** 36%

Scheme 120 Manganese dioxide oxidation of α-vinyl benzyl alcohol

However, in both solvent systems an impure product was obtained; for example after 72 hours in ethyl acetate 3-phenyl-1-propen-3-one **183** was obtained as a pale yellow oil in only 36% yield. The ^{1}HMR data was inconclusive, but appeared to indicate the presence of a number of unidentified polymeric products. This fact was reinforced by the TLC analysis, which indicated that the product deteriorated over time.

A second approach towards the synthesis of 3-phenyl-1-propen-3-one **183** provided less rewarding results. It was proposed that the simple Friedel-Crafts acylation[22] between benzene and acryloyl chloride **184** should afford 3-phenyl-1-propen-3-one **183** in good yield (Scheme 121).

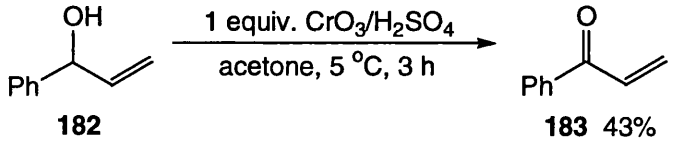


184 **183**

Scheme 121 Attempted formation of 3-phenyl-1-propen-3-one

However, after only 20 minutes at room temperature the major (100% consumption of starting material) product displayed analytical data consistent with an unidentified polymeric product; *m/z* data suggested that the ring-closed species, indan-2-one, was also present.

Thus, in order to obtain an improved conversion into 3-phenyl-1-propen-3-one **183**, the Jones oxidation[29] of α-vinyl benzyl alcohol **182** was attempted (Scheme 122); a procedure which does have literature precedent.[30,31]

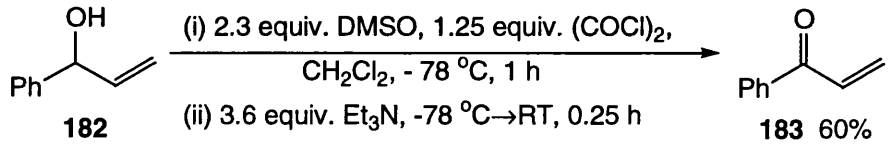


182 **183** 43%

Scheme 122 Jones oxidation of α-vinyl benzyl alcohol

However, although the crude ^{1}HMR delineated a much 'cleaner' reaction profile, only a moderate yield (43%) of 3-phenyl-1-propen-3-one **183** as a colourless oil was obtained after column chromatography.

Motherwell *et al.*[32] demonstrated that 3-phenyl-1-propen-3-one **183** could be prepared in moderate yield *via* the Swern oxidation of freshly prepared α-vinyl benzyl alcohol **182** (Scheme 123).

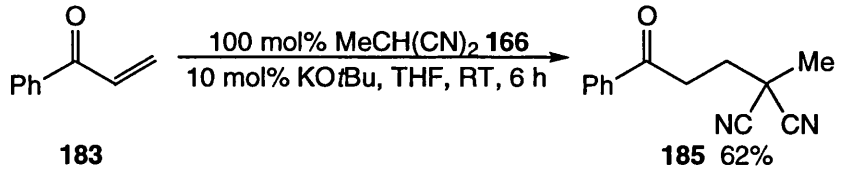


182 **183** 60%

Scheme 123 Swern oxidation of α-vinyl benzyl alcohol

Thus, it was possible to prepare 3-phenyl-1-propen-3-one **183** in a moderate yield (60%), which compared favourably with that of Motherwell *et al.* (66%). However it *was* noticed that the colourless oil had a tendency to darken on standing at room temperature.

Nevertheless, 3-phenyl-1-propen-3-one **183** proved to be an excellent Michael acceptor in reaction with the nucleophile derived from methylmalononitrile **166** (Scheme 124).

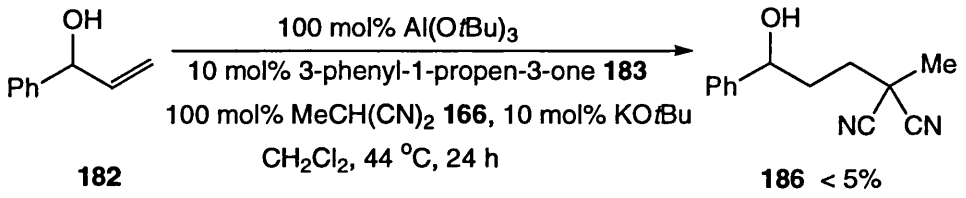


183 **185** 62%

Scheme 124 Michael addition of methylmalononitrile to 3-phenyl-1-propen-3-one

After purification and recrystallisation from ether, 2-methyl-2-(3-oxo-3-phenyl-propyl)-malononitrile **185** was obtained as a white needle-like crystalline solid in 62% yield. The identity of the novel compound was confirmed by ^{13}C analysis, which indicated both the presence of the carbonyl (196 ppm) and the nitrile functionalities (116 ppm).

It was hoped that the formation of the thermodynamically more favourable conjugated ketone, would ensure a constant supply of enone ready for conjugate addition in the linear allylic alcohol CEA procedure, however α-vinyl benzyl alcohol **182** was demonstrated to be a poor substrate: < 5% conversion after 24 hours (Scheme 125).



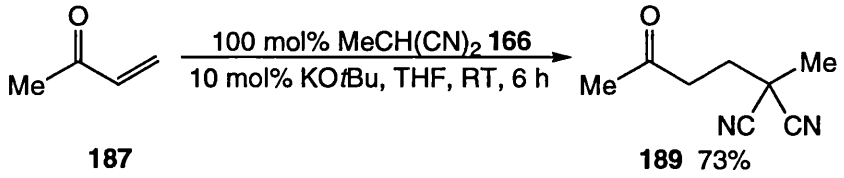
182 **186** < 5%

Scheme 125 α-Vinyl benzyl alcohol domino Oppenauer/Michael addition/MPV reaction

A possible explanation of the problems associated with the synthesis, purification and subsequent use of 3-phenyl-1-propen-3-one **183** were proposed by Reich and Renga[33] who demonstrated that "acrylophenone [was] an olefin unusually sensitive to polymerisation and nucleophilic attack". Furthermore, Motherwell indicated[32] that 3-phenyl-1-propen-3-one **183** was prepared and "used directly". Thus, it was decided that a more robust starting material should be investigated.

The commercially available, methyl vinyl ketone **187**, appeared a promising alternative. Whilst the low boiling point of this substrate and its alcohol precursor, 3-buten-2-ol **188** would present some difficulties, it was proposed that the corresponding Michael addition adducts would be solid products and therefore feasible for conversion studies. Thus freshly distilled methyl vinyl ketone **187** was efficiently transformed into 2-methyl-2-(3-oxo-butyl)-malononitrile **189**, a white solid, in 73% yield after purification (Scheme 126). The structure of ketone (**189**) was

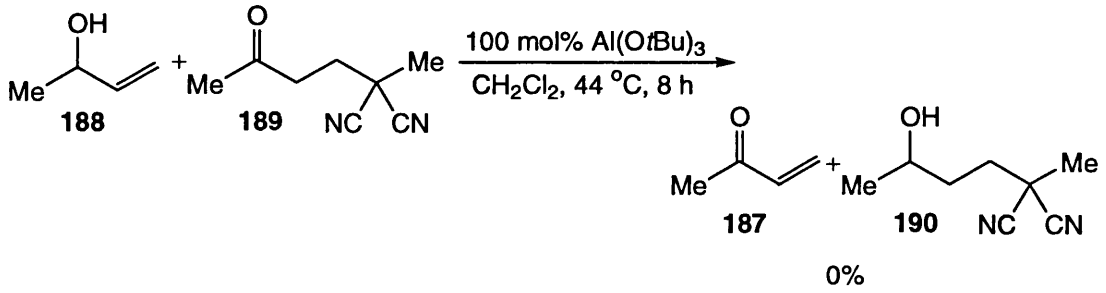
confirmed by ^{13}C NMR, which indicated both the nitrile (120 ppm) and carbonyl functionalities (196 ppm) were present.



187 **189** 73%

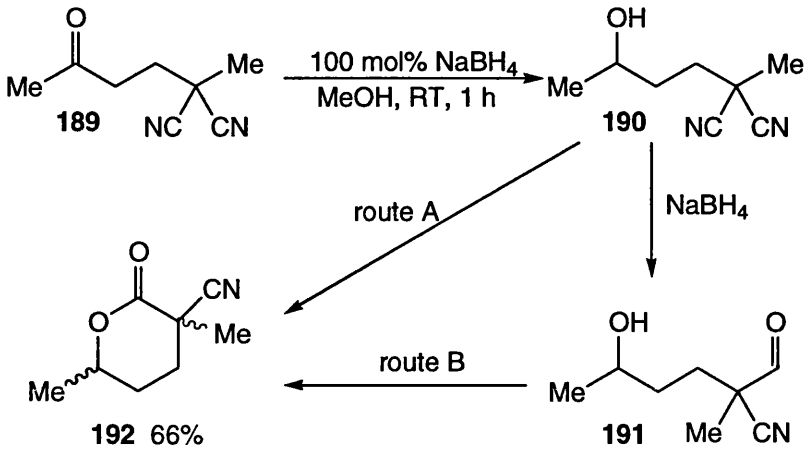
Scheme 126 Michael addition of methylmalononitrile to methyl vinyl ketone

The domino Oppenauer/Michael addition/MPV process using α-vinyl benzyl alcohol **182** had demonstrated it was unrealistic to assume that the formation of the conjugated ketone from the allylic alcohol was always an efficient procedure. Thus, when 3-buten-2-ol **188** and ketone (**189**) were subjected to the crossover transfer hydrogenation conditions, a 0% conversion into the corresponding alcohol derivative (**190**) was obtained (Scheme 127).



Scheme 127 Aluminium catalysed Oppenauer/MPV crossover reaction

In order to try and rationalise this result, an alternative synthesis of 2-(3-hydroxy-butyl)-2-methyl-malononitrile **190** was attempted in order to compare the ^{1}H NMR data (Scheme 128).

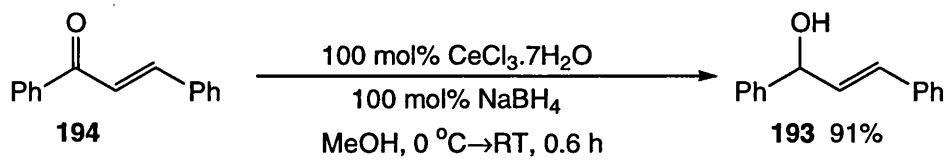


Scheme 128 Sodium borohydride reduction of 2-methyl-2-(3-oxo-butyl)-malononitrile

Somewhat surprisingly, after purification, the two isolated products appeared to be consistent with the diastereomeric lactones (**192**) (Scheme 128). Furthermore, the identity of these compounds was confirmed by high resolution mass spectrometry (HRMS) (M+H, 154.0854 Da), ^{13}C HMR and IR data (C=O, 175 ppm; 1725 cm^{-1}). However, what was not conclusive was whether the formation of the lactone product was through the sluggish hydride-mediated conversion of a nitrile group into an aldehyde.[8-10] and subsequent lactonisation (Scheme 128, route B), or whether the reaction proceeded *via* direct alcoholysis of the nitrile (Scheme 128, route A).[21] Lactone formation *via* an intramolecular Pinner reaction does have literature precedent.[34] However, both the extremely poor conversion of the allylic alcohol (**188**) into the corresponding conjugated ketone (**187**) coupled with the possibility of lactonisation suggested that an alternative substrate should be sought.

As a result, the final study towards the linear allylic alcohol CEA procedure probed the use of (*E*)-1,3-diphenyl-prop-2-en-1-ol **193** derived substrates. As a consequence, the substitution at the double bond terminus *would* lead to a diastereomeric product ratio, however it was proposed that this disadvantage would be offset by the formation of a highly conjugated ketone intermediate, (*E*)-1,3-diphenyl-prop-2-en-1-one (chalcone) **194**.

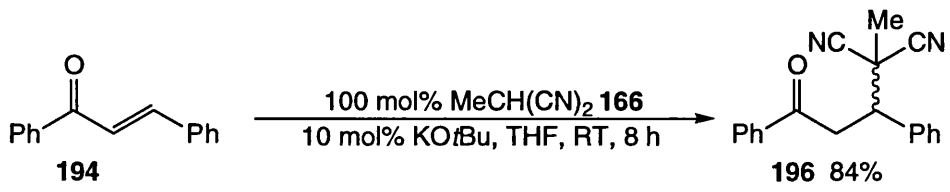
(*E*)-1,3-diphenyl-prop-2-en-1-ol **193** was not commercially available, but was easily prepared as a white solid, after recrystallisation, from chalcone **194** using a facile Luche reduction[15] (Scheme 129).



Scheme 129 Synthesis of (*E*)-1,3-diphenyl-prop-2-en-1-ol

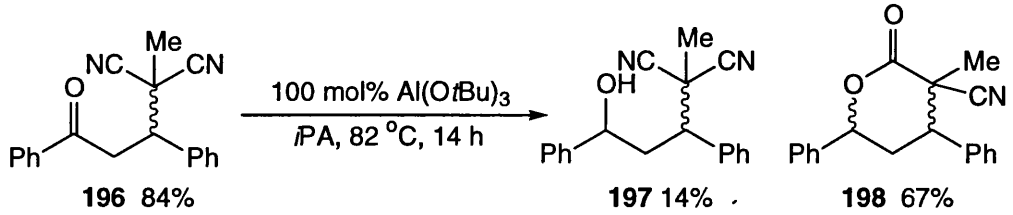
The thermodynamic driving force to form the conjugated ketone (**194**) was highlighted by the observed conversion of (*E*)-1,3-diphenyl-prop-2-en-1-ol **193** into chalcone **194** over time *via* an aerial oxidation reaction at room temperature.

The initial focus of the study was to determine whether chalcone **194** could act as a Michael acceptor in reaction with methylmalononitrile **166.** Thus, recrystallised chalcone (commercially available starting material was found to contain a small amount (< 10%) of 1,3,5-triphenylpentan-1,5-dione **195**[35]) was efficiently converted into 2-methyl-2-(3-oxo-1,3-diphenyl-propyl)-malononitrile **196** as a white crystalline solid (apparent single diastereomer due to restricted conformation), in 84% yield after purification (Scheme 130).[36] The identify of the product (**196**) was confirmed by HRMS (288.1262 Da) and ^{13}C analysis which indicated the presence of the carbonyl (195 ppm) and nitrile groups (116 and 118 ppm).



Scheme 130 Formation of 2-Methyl-2-(3-oxo-1,3-diphenyl-propyl)-malononitrile

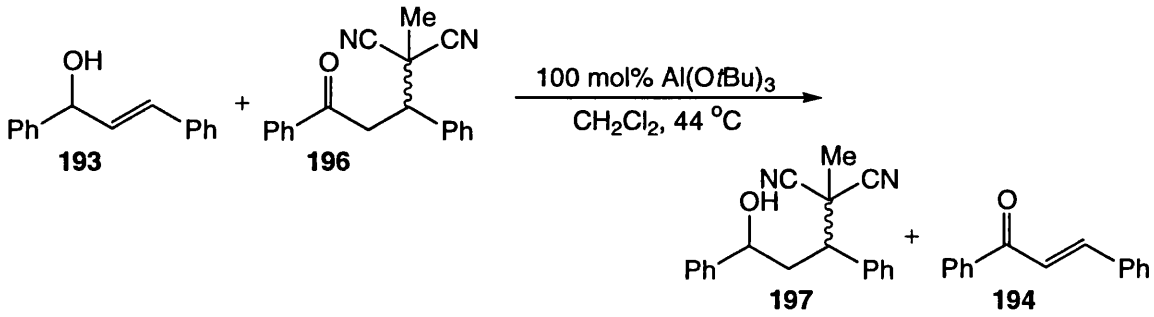
In order to order to prevent the myriad of problems encountered with hydride-based reducing agents (*vide supra*), the reduction of ketone (**196**) into the corresponding alcohol derivative (**197**) was attempted under MPV-type conditions (Scheme 131).



Scheme 131 MPV reduction of 2-methyl-2-(3-oxo-1,3-diphenyl-propyl)-malononitrile

After purification, three products were isolated from the MPV reduction: as anticipated the alcohol (**197**) (*m/z* 290.1419 Da) was only formed in a low yield (14%) after 14 hours at reflux and, furthermore, the main products of the reaction were found to be consistent with the diastereomeric lactones (**198**) (*m/z* 291.1259 Da). Although disappointing, this result did confirm that the lactone products (**198**) could be formed *via* an intramolecular nitrile alcoholysis reaction (Scheme 128, route A),[34] rather than exclusively through sodium borohydride mediated nitrile reduction and lactonisation (Scheme 128, route B). Nevertheless, the formation of the lactone products (**198**), and therefore the concomitant formation of the corresponding alcohol precursors (**197**) does indicate that an MPV-type reduction of ketone (**196**) is feasible.

Therefore the crossover transfer hydrogenation between (*E*)-1,3-diphenyl-prop-2-en-1-ol **193** and ketone (**196**) was attempted (Scheme 132, Table 15).



Scheme 132 Aluminium catalysed Oppenauer/MPV crossover reaction

Entry	$Al(OtBu)_3$ [mol%][a]	CH_2Cl_2 [mL]	*t* [h]	Conversion [%][b]
1	100	10	8	10
2	100	5	24	23
3	100	5	110	28

[a] Reactions were performed on a 1 mmol scale in solvent at reflux. [b] Analysed by ^1H NMR.
Table 15 Results of aluminium catalysed Oppenauer/MPV crossover reaction

However, even after prolonged reaction times (Table 15, entry 3) a very poor conversion into the alcohol adduct (**197**)/chalcone **194** was obtained. It is difficult to rationalise mechanistically why this is the case, however it is proposed that the steric bulk of both the *oxidant* and *reductant* hinders the formation of the necessary six-membered MPV transition state, and thus hydride transfer is an inefficient process (Figure 12).

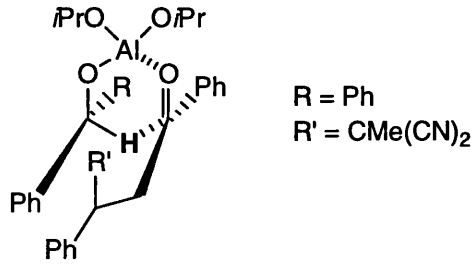
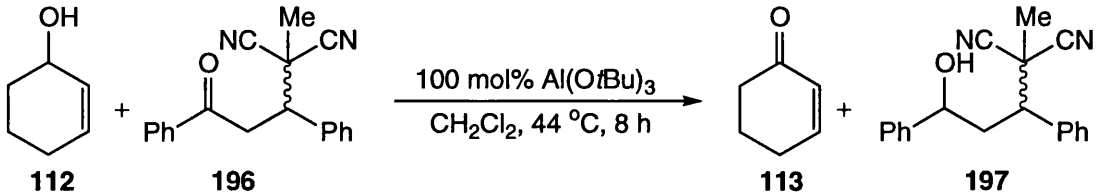


Figure 12 Proposed chalcone MPV transition state

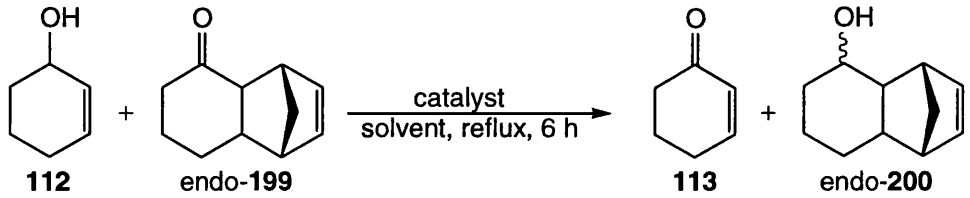
In an attempt to reduce the steric bulk around the aluminium centre, the reaction was repeated using a 1:1 mixture of 2-cyclohexen-1-ol **112** and ketone (**196**) (Scheme 133).



Scheme 133 Aluminium catalysed Oppenauer/MPV crossover reaction

However, whilst isopropanol was demonstrated to be an efficient reductant (Scheme 131), 2-cyclohexen-1-ol **112** did not improve the conversion to alcohol (**195**). This was interesting as 2-cyclohexen-1-ol **112** has been shown to be an excellent reductant in all crossover transfer hydrogenations attempted thus far.

This result mirrors recent work towards a domino Oppenauer/Diels-Alder/MPV process[37] in which the bicyclic hindered endo-ketone (**199**) was demonstrated to be inert to the crossover transfer hydrogenation with 2-cyclohexen-1-ol **112** (Scheme 134).



25 mol% $Al(OtBu)_3$, CH_2Cl_2, 44 °C < 5%

10 mol% $La(OiPr)_3$, THF, 66 °C 0%

Scheme 134 Diels-Alder crossover Oppenauer/MPV process

It would therefore appear that a methylmalononitrile **166** nucleophile and a linear allylic alcohol substrate are not feasible reactants in the domino/Michael addition/MPV process.

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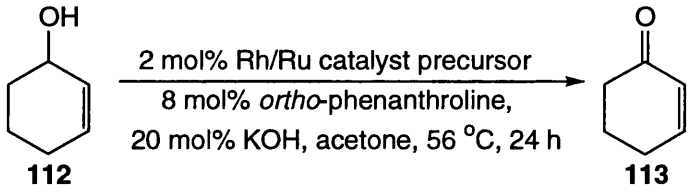
Chapter 4

4.1 Transition Metal Catalysed Oxidation and Reduction Reactions

Earlier work within the group[1] indicated that transfer hydrogenation reactions could be carried out using a transition metal, coupled with an *ortho*-phenanthroline ligand and catalytic amounts of base.[2] Therein, it was demonstrated that the active catalyst was able to effect racemisation of an enantiomerically pure alcohol *via* the corresponding carbonyl intermediate, using an acetone/isopropanol solvent system. In addition the catalyst appeared promising in that it was able to perform both the oxidation *and* reduction reactions and importantly, was base-stable, a prerequisite for the Michael addition. It was therefore proposed that an acetone/isopropanol solvent system would allow both the *activation* and subsequent reduction reactions to occur in *one-pot*, thus enabling the CEA process to proceed to completion.

Herein, the use of three common rhodium catalyst precursors: $[Rh(OAc)_2]_2.2H_2O$, $[RhCl(\eta^4\text{-}1,5\text{-hexadiene})]_2$ and $[Rh(COD)Cl]_2$ plus the ruthenium pre-catalyst, $RuCl_2(PPh_3)_3$, were investigated (Table 16). Preliminary studies were concentrated upon the oxidation of 2-cyclohexen-1-ol **112** with acetone as the oxidant. The active catalyst was first prepared by stirring the ligand/catalyst (4:1 ratio) together in excess acetone for 15 minutes prior to the addition of the alcohol and potassium hydroxide (Scheme 135).



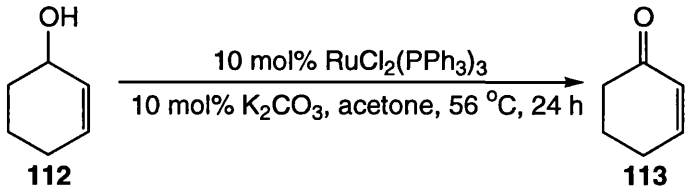
Scheme 135 Ruthenium/rhodium catalysed oxidation of 2-cyclohexen-1-ol

Entry	Pre-catalyst[a] [mol%]	Base [mol%]	*t* [h]	Conversion [%][b]
1	$[Rh(OAc)_2]_2.2H_2O$ (2.0)	KOH (20)	24	15
2	$RuCl_2(PPh_3)_3$ (2.0)	KOH (20)	24	26
3	$[RhCl((\eta^4\text{-}1,5\text{-hexadiene})]_2$ (2.0)	KOH (20)	24	8
4	$[Rh(COD)Cl]_2$ (2.0)	KOH (20)	24	13

[a] The reactions were carried out on a 1 mmol scale in acetone (5 mL) at reflux. [b] Analysed by HPLC.

Table 16 Results of the transition metal catalysed oxidation of 2-cyclohexene-1-ol

The conversion into 2-cyclohexen-1-one **113** was determined by HPLC analysis. Confirmation of the product's identity was obtained by FT-IR (conjugated carbonyl peak at 1685 cm^{-1}), however the precatalysts screened all realised a poor conversion into product (Table 16); nevertheless the ruthenium catalyst did appear to be superior to the rhodium species. In support of this proposal, a recent study by Bäckvall and co-workers[3] demonstrated that $RuCl_2(PPh_3)_3/K_2CO_3$ efficiently catalysed the oxidation of alcohols in the absence of a ligand. Therefore, in order to try and improve the conversion into ketone (**113**), the oxidation of 2-cyclohexen-1-one **113** was attempted using Bäckvall's catalyst system (Scheme 136, Table 17).



112 **113**

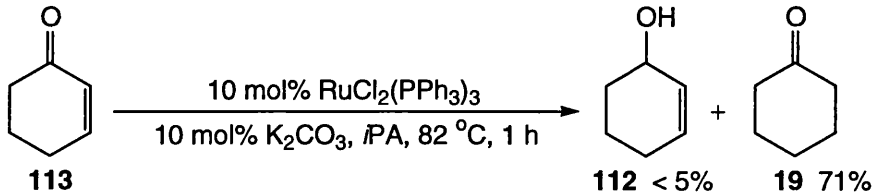
Scheme 136 Oxidation of 2-cyclohexen-1-ol using Bäckvall's conditions

Entry	$RuCl_2(PPh_3)_3$ [mol%][a]	K_2CO_3 [mol%]	*t* [h]	Conversion [%][b]
1	1	10	12	0
2	5	10	12	23
3	10	10	24	40
4	20	10	24	44

[a] The reactions were carried out on a 1 mmol scale in acetone (5 mL) at reflux. [b] Analysed by ^1H NMR.

Table 17 Oxidation of 2-cyclohexen-1-ol using Bäckvall's catalyst system

Yet the results from the use of Bäckvall's oxidation conditions were somewhat disappointing (Table 17). Although the conversions were improved at higher catalyst loadings (Table 17, entries 3 and 4), they are still rather low.[3] A possible explanation for this was provided by the attempted reduction of 2-cyclohexen-1-one **113** using $RuCl_2(PPh_3)_3$ (Scheme 137).



113 **112** < 5% **19** 71%

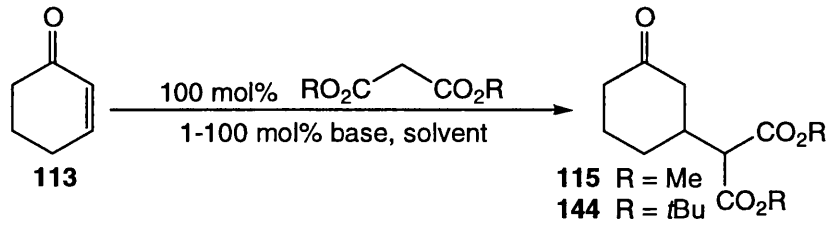
Scheme 137 Reduction of 2-cyclohexen-1-one using Bäckvall's conditions

Analysis (^{1}H NMR) of the crude reaction mixture indicated that although the 2-cyclohexen-1-one **113** starting material had all been consumed, the desired product had not been obtained. Further inspection indicated that the main product was consistent with cyclohexanone in a 71% conversion, whilst a small amount (10%) of cyclohexanol **17** was also observed. In addition, at higher conversions it was noted that the ratio of cyclohexanol: cyclohexanone increased.[2] It might therefore be reasonable to assume that the low conversions noted for the oxidation of 2-cyclohexen-1-ol **112** by $RuCl_2(PPh_3)_3$ are due to the formation of cyclohexanone **19** *via* ruthenium-catalysed double bond migration (*vide supra*).[4] It was for this reason that we chose to explore aluminium (MPV-type) catalysts for their ability to effect transfer hydrogenation selectively.

4.2 Miscellaneous Michael Addition Reactions

In the course of this study a wide selection of catalysts were evaluated for the Michael addition[5] of malonate-type nucleophiles to 2-cyclohexen-1-one **113**. Thus, in conjunction with the familiar inorganic bases (sodium hydride and potassium *tert*-butoxide), the role of fluoride, organic and aluminium reagents have also been investigated for their ability to mediate the Michael addition reaction.

As the project progressed, so did the parallel Michael addition chemistry. Therefore, the first reactions evaluated were those using dimethyl- (**114**) and di-*tert*-butyl (**146**) malonate derived nucleophiles (Scheme 138, Table 18).



Scheme 138 Comparison of inorganic and organic base mediated Michael addition

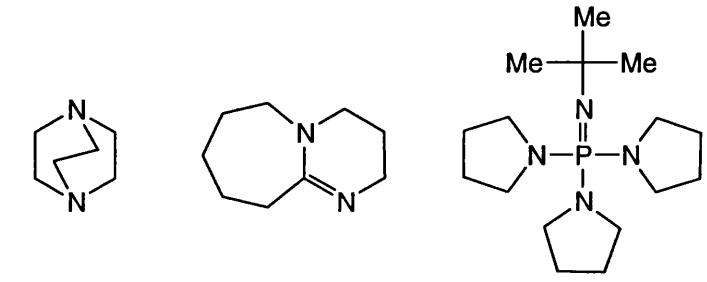
Entry	Base[a] [mol%]	R	Solvent [mL]	Temp. [°C]	*t* [h]	Conversion [%][b]
1	NaH (10)	Me	MeOH (10)	25	5.5	> 90
2	KO*t*Bu (10)	*t*Bu	THF (10)	25	6.5	> 90
3	Al(O*t*Bu)$_3$ (100)	*t*Bu	CH_2Cl_2 (10)	50	18	4[c]
4	Me_2AlCl (100)	*t*Bu	CH_2Cl_2 (5)	25	18	< 5
5	Phosphazene (1)[d]	Me	THF (10)	25	24	> 90
6	Phosphazene (1)[d]	Me	C_6H_{12} (10)	25	24	7[c]
7	Phosphazene (10)[d]	*t*Bu	THF (10)	25	4	0
8	DABCO (10)[e]	*t*Bu	THF (10)	25	4	0
9	DBU (10)[f]	*t*Bu	THF (10)	25	4	0

[a] The reactions were carried out on a 1 mmol scale. [b] Analysed by ^{1}H NMR. [b] Analysed by ^{1}H NMR spectroscopy. [c] Yield of isolated product after flash column chromatography. [d] *tert*-Butylimino-tri(pyrrolidino)phosphorane. [e] 1,4-Diazabicyclo[2.2.2]octane. [f] 1,8-Diazabicyclo[5.4.0]undec-7-ene.

Table 18 Comparison of inorganic and organic base mediated Michael addition

As anticipated, the inorganic bases sodium hydride and potassium *tert*-butoxide provided excellent conversion with both nucleophiles (Table 18, entries 1 and 2).

However, a catalytic amount of sterically hindered phosphorus-nitrogen base **(203)**[6] also provided an excellent conversion to ketone **(115)** (Table 18, entry 5). Conversely, the use of phosphazene base **(203)** and both DABCO **201** and DBU **202** with di-*tert*-butyl malonate **146** (Table 18, entries 7-9) was unsuccessful. It is unrealistic to assume that the strongly basic[6] phosphazene **(203)** is unable to deprotonate the *tert*-butyl malonate substrate **146** and therefore, that it is the complex formed between the sterically hindered organic base and di-*tert*-butyl malonate **146** that is unreactive towards 2-cyclohexen-1-one **113**.

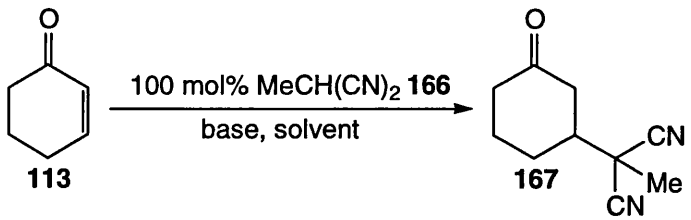


DABCO **201** DBU **202** Phosphazene **203**

Figure 13 Structure of sterically hindered organic bases

Furthermore, the Michael addition reaction of di-*tert*-butyl malonate **146** and 2-cyclohexen-1-one **113** in the presence of aluminium *tert*-butoxide was attempted *without* the addition of base (Table 18, entry 3). However, after 18 hours at reflux only a 4% isolated yield of product was obtained. This property was reflected by dimethylaluminium chloride (Table 18, entry 4), which was equally ineffective.

As the project progressed and attention focussed towards malononitrile **166** derived nucleophiles, the use of fluoride bases, in addition to organic bases (Figure 13) was introduced (Scheme 139, Table 19).



113 **167**

Scheme 139 Comparison of aluminium, fluoride and organic base mediated Michael addition

Entry	Base[a] [mol%]	Solvent [mL]	Temp. [°C]	*t* [h]	Conversion [%][b]
1	KO*t*Bu (1)	CH_2Cl_2 (5)	25	72	> 95
2	NaO*t*Bu (10)	THF (5)	25	6	83[c]
3	Me_2AlCl (11)	THF (5)	25	72	< 5
4	CsF (10)	THF (5)	25	72	> 90
5	CsF (100)	THF (5)	25	72	> 90
6	Phosphazene (10)[d]	THF (5)	25	24	94
7	DABCO (10)[e]	THF (5)	25	24	< 5
8	DBU (10)[f]	THF (5)	25	24	89
9	Imidazole (10)	THF (5)	25	24	71

[a] The reactions were carried out on a 1 mmol scale. [b] Analysed by ^{1}H NMR. [b] Analysed by ^{1}H NMR spectroscopy. [c] Yield of isolated product after flash column chromatography. [d] *tert*-Butylimino-tri(pyrrolidino)phosphorane. [e] 1,4-Diazabicyclo[2.2.2]octane. [f] 1,8-Diazabicyclo[5.4.0]undec-7-ene.

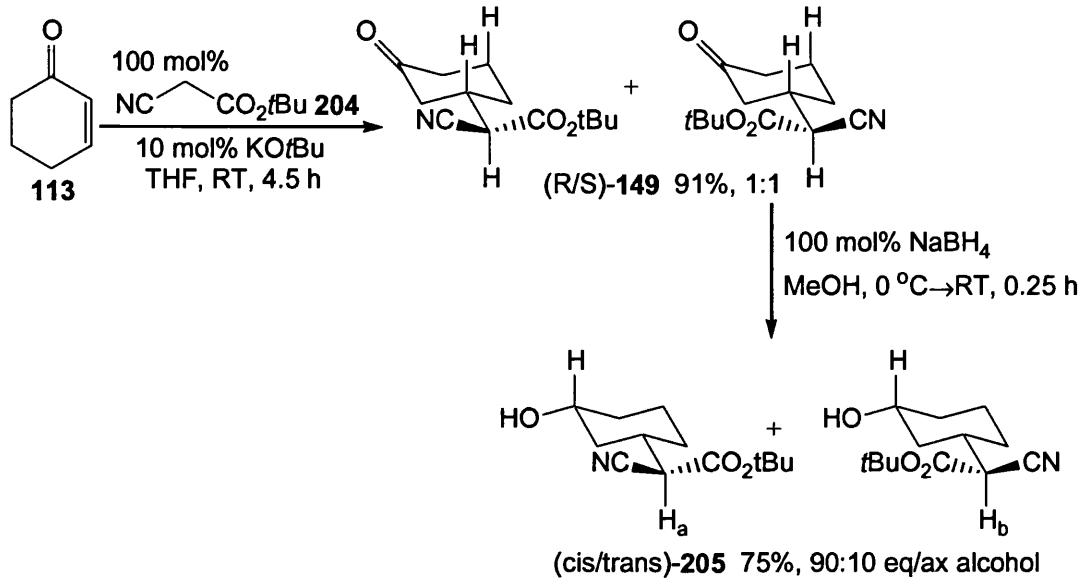
Table 19 Results of comparison of aluminium, fluoride and organic base mediated Michael addition

Thus, the inorganic bases potassium and sodium *tert*-butoxide were again demonstrated to be excellent catalysts in the Michael addition reaction, even with loadings as low as 1 mol% (Table 19, entry 2), although this did necessitate prolonged reaction times. The acidity of the methylmalononitrile **166** α-proton (pK_a 11.2)[7] does not differ greatly from that of the di-*tert*-butyl malonate **146** (pK_a 11.6)[7] α-proton, yet phosphazene (**203**), DBU **202** and imidazole bases (Table 19, entries 6, 8 and 9), in contrast to the analogous reaction (*vide supra*), are all able to catalyse the desired Michael addition reaction efficiently. In addition caesium fluoride exhibited excellent activity (rate studies indicated the reaction reached near completion after 8 hours) at substoichiometric levels (Table 19, entries 4 and 5), a property not normally associated with fluoride bases.[8] However, both dimethylaluminium chloride (Table 4, entry 3) and the weaker organic base, DABCO **201**, proved to be inefficient catalysts (Table 19, entry 7).

Thus, as an alternative to inorganic catalysts, both organic and fluoride bases were demonstrated to be viable efficient alternatives; a property thus exploited in the 2-cyclopenten-1-ol **112** domino Oppenauer/Michael addition/MPV process (Chapter 3, section 3.2).

4.3 Towards the addition of *tert*-Butylcyanoacetate to an Allylic Alcohol

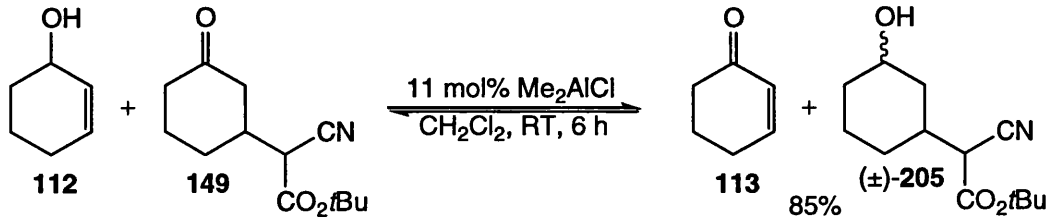
In conjunction with the research into malononitrile **166** derivatives, a separate parallel study focussed on the use of *tert*-butylcyanoacetate **204**. Thus, both the ketone (**149**)[9] and alcohol adducts (cis/trans-**205**) were prepared using analogous methodology to that previously described (Scheme 140).



Scheme 140 Formation of *tert*-butylcyanoacetate derivatives

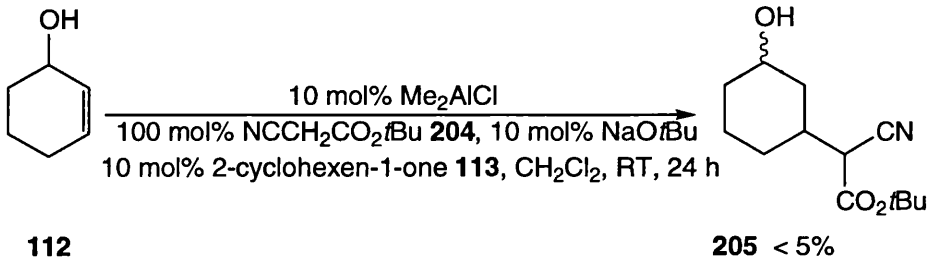
In contrast to the symmetrical methylmalononitrile **166**, the use of the unsymmetrical *tert*-butylcyanoacetate nucleophile **204**, leads ultimately to a potentially complex mixture of diastereomeric alcohol derivatives. However, the interpretation of the ^{1}H NMR data is simplified by two factors: firstly the *tert*-butylcyanoacetate group will preferentially favour an equatorial conformation (A value ~ 21 kJ mol^{-1}),[10] secondly for the comparatively unhindered substrate (**149**) there is a tendency for approach of the hydride to the carbonyl group in an axial direction, leading to the equatorial alcohol.[11] Thus, the mixture of cis-1,3 diastereomeric products (cis/trans-**205**) was identified by the presence of a pair of doublets corresponding to H_a/H_b and a single CH-OH multiplet in the ^{1}H NMR (Scheme 140).

As anticipated, ketone (**149**) was efficiently converted into the diastereomeric alcohols (cis/trans-**205**) through a dimethylaluminium chloride catalysed crossover transfer hydrogenation reaction (Scheme 141).



Scheme 141 Oppenauer/MPV crossover

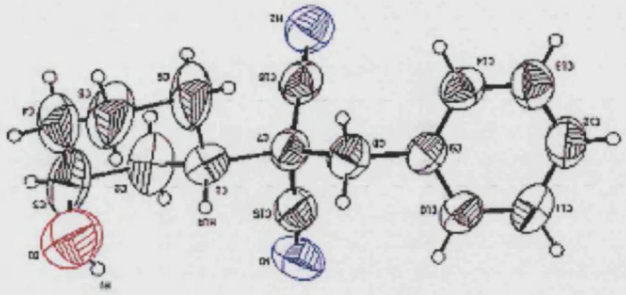
These data clearly demonstrate that the equilibrium position for the transfer hydrogenation reaction lies towards the thermodynamically more favourable conjugated ketone. Thus, based on the conditions needed for conjugate addition and for transfer hydrogenation an indirect nucleophilic addition of *tert*-butylcyanoacetate **204** to 2-cyclohexen-1-one **113** was attempted (Scheme 142).



Scheme 142 *tert*-Butylcyanoacetate domino Oppenauer/Michael addition/MPV process

However, *tert*-butylcyanoacetate **204** proved to be an inefficient nucleophile in the domino Oppenauer/Michael addition/MPV process, providing less than five percent conversion into the desired alcohol (**205**). It is difficult to reason mechanistically why *tert*-butylcyanoacetate **204** should provide such a poor conversion into product, however, it is proposed that a combination of both the steric bulk and possible catalyst co-ordination retards the reactivity. Nevertheless, it was anticipated that this substrate should warrant future work.

4.4 X-Ray data: trans-2-Benzyl-2-(3-hydroxy-cyclohexyl)-malononitrile; trans-171



Identification code	k01jmjw3
Empirical formula	$C_{16}H_{18}N_2O$
Formula weight	254.32
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_1cn$
Unit cell dimensions	a = 8.3190(3) Å α = 90 °
	b = 9.8610(3) Å β = 90 °
	c = 17.6680(7) Å γ = 90 °
Volume	1449.37(9) $Å^3$
Z	4
Density (calculated)	1.166 Mg m^{-3}
Absorption coefficient	0.074 mm^{-1}
F(000)	544
Crystal size	0.50 x 0.20 x 0.20 mm
Theta range for data collection	3.95 to 24.98 °
Index ranges	-8<=h<=9; -11<=k<=11; -20<=l<=20
Reflections collected	17371
Independent reflections	2466 [R(int) = 0.0761]
Reflections observed (>2σ)	1514
Data Completeness	0.993
Max. and min. transmission	0.9854 and 0.9641

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2466 / 44 / 238
Goodness-of-fit on F^2	1.017
Final R indices [I>2σ(I)]	R_1 = 0.0839 wR_2 = 0.2287
R indices (all data)	R_1 = 0.1257 wR_2 = 0.2651
Absolute structure parameter	-5(8)
Largest diff. peak and hole	0.207 and -0.177 eÅ^{-3}

Table 20 Crystal data and structure refinement for k01jmjw3

Notes: poorly diffracting crystal at higher Bragg angles. Hydroxylated cyclohexyl group exhibits positional disorder in ratio 60:40. ADPs of atoms therein and bond distances refined subject to constraints. This refinement would be likely to benefit from recollection of data at 150 K.

Atom	x	y	z	U [eq]
O(1)	89(16)	5867(17)	5121(9)	222(5)
O(101)	-3040(20)	6080(20)	3676(8)	207(7)
N(1)	3870(9)	3947(6)	3271(3)	146(2)
N(2)	35(7)	4287(6)	1680(3)	142(2)
C(1)	676(12)	6020(10)	3532(7)	105(3)
C(2)	28(18)	4878(11)	3906(8)	149(4)
C(3)	-857(16)	5141(11)	4713(8)	158(3)
C(4)	-2160(20)	6270(19)	4486(9)	168(5)
C(5)	-1680(20)	7282(19)	4077(10)	206(8)
C(6)	-812(18)	6770(20)	3258(8)	236(10)
C(101)	306(19)	5880(20)	3241(7)	133(7)
C(102)	-760(30)	4984(19)	3516(9)	147(5)
C(103)	-2120(20)	5419(19)	4104(9)	161(6)
C(104)	-1260(30)	6490(20)	4629(9)	149(7)
C(105)	-460(20)	7513(15)	4339(9)	139(5)
C(106)	1070(16)	6670(30)	3926(9)	212(11)
C(7)	1672(6)	5574(5)	2730(3)	99(1)
C(8)	2479(7)	6834(5)	2376(3)	107(2)
C(9)	3561(6)	6520(4)	1699(3)	95(1)
C(10)	5126(7)	6232(6)	1792(3)	115(2)
C(11)	6098(8)	5978(7)	1168(4)	131(2)
C(12)	5431(9)	6020(8)	450(4)	136(2)
C(13)	3917(9)	6318(6)	362(4)	131(2)
C(14)	2948(7)	6593(5)	976(3)	113(2)
C(15)	2909(8)	4648(6)	3021(3)	110(2)
C(16)	769(7)	4846(6)	2137(3)	110(2)

Table 21 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for k01jmjw3

U (eq) is defined as one third of the trace of the orthogonalised Uij tensor

O(1)-C(3)	1.285(14)	O(101)-C(103)	1.256(19)
N(1)-C(15)	1.145(7)	N(2)-C(16)	1.153(7)
C(1)-C(2)	1.413(13)	C(1)-C(6)	1.522(14)
C(1)-C(7)	1.699(12)	C(2)-C(3)	1.626(14)
C(3)-C(4)	1.603(17)	C(4)-C(5)	1.293(17)
C(5)-C(6)	1.694(18)	C(101)-C(102)	1.345(17)
C(101)-C(7)	1.483(16)	C(101)-C(106)	1.574(11)
C(102)-C(103)	1.595(18)	C(103)-C(104)	1.578(18)
C(104)-C(105)	1.315(17)	C(105)-C(106)	1.681(19)
C(7)-C(15)	1.469(9)	C(7)-C(16)	1.474(8)
C(7)-C(8)	1.544(7)	C(8)-C(9)	1.528(7)
C(9)-C(10)	1.343(7)	C(9)-C(14)	1.378(7)
C(10)-C(11)	1.391(8)	C(11)-C(12)	1.384(9)
C(12)-C(13)	1.303(10)	C(13)-C(14)	1.378(9)
C(2)-C(1)-C(6)	103.1(11)	C(2)-C(1)-C(7)	111.7(8)
C(6)-C(1)-C(7)	105.0(9)	C(1)-C(2)-C(3)	117.1(9)
O(1)-C(3)-C(4)	99.6(13)	O(1)-C(3)-C(2)	107.7(11)
C(4)-C(3)-C(2)	101.4(10)	C(5)-C(4)-C(3)	118.0(13)
C(4)-C(5)-C(6)	112.2(14)	C(1)-C(6)-C(5)	102.8(10)
C(102)-C(101)-C(7)	126.1(16)	C(102)-C(101)-C(106)	108.4(13)
C(7)-C(101)-C(106)	105.1(10)	C(101)-C(102)-C(103)	121.7(14)
O(101)-C(103)-C(104)	106.6(18)	O(101)-C(103)-C(102)	100.2(15)
C(104)-C(103)-C(102)	103.9(12)	C(105)-C(104)-C(103)	121.0(13)
C(104)-C(105)-C(106)	100.0(15)	C(101)-C(106)-C(105)	105.8(12)
C(15)-C(7)-C(16)	107.6(4)	C(15)-C(7)-C(101)	116.8(9)
C(16)-C(7)-C(101)	98.2(5)	C(15)-C(7)-C(8)	109.7(4)
C(16)-C(7)-C(8)	109.0(4)	C(101)-C(7)-C(8)	114.5(9)
C(15)-C(7)-C(1)	102.1(5)	C(16)-C(7)-C(1)	118.0(5)
C(101)-C(7)-C(1)	20.9(5)	C(8)-C(7)-C(1)	109.9(5)
C(9)-C(8)-C(7)	114.2(4)	C(10)-C(9)-C(14)	118.9(5)
C(10)-C(9)-C(8)	121.2(5)	C(14)-C(9)-C(8)	119.8(5)
C(9)-C(10)-C(11)	120.3(6)	C(12)-C(11)-C(10)	119.2(6)
C(13)-C(12)-C(11)	120.3(6)	C(12)-C(13)-C(14)	121.0(7)
C(9)-C(14)-C(13)	120.3(6)	N(1)-C(15)-C(7)	177.7(6)
N(2)-C(16)-C(7)	178.6(6)		

Table 22 Bond lengths [Å] and angles [°] for k01jmjw3

Symmetry transformations used to generate equivalent atoms:

Atom	U11	U22	U33	U23	U13	U12
O(1)	180(9)	261(12)	223(9)	-79(9)	9(9)	4(8)
O(101)	182(11)	320(20)	124(9)	-89(11)	11(7)	-5(12)
N(1)	162(5)	162(5)	114(3)	3(3)	-26(3)	36(4)
N(2)	131(4)	143(4)	152(4)	10(3)	-11(4)	-45(3)
C(1)	92(6)	100(5)	121(8)	-8(5)	-6(5)	-1(4)
C(2)	170(10)	96(5)	180(8)	-2(5)	54(7)	3(5)
C(3)	164(9)	108(6)	202(9)	-21(5)	76(7)	-29(5)
C(4)	173(10)	201(13)	131(10)	-30(8)	58(7)	16(8)
C(5)	150(13)	231(17)	238(15)	47(12)	78(12)	69(12)
C(6)	160(11)	340(20)	205(11)	136(12)	94(10)	149(15)
C(101)	83(9)	255(17)	60(6)	-79(8)	1(5)	-67(9)
C(102)	200(13)	140(12)	101(9)	-31(8)	30(9)	-33(8)
C(103)	193(13)	200(16)	90(9)	-15(8)	57(7)	-88(11)
C(104)	198(13)	192(15)	57(6)	-20(6)	37(6)	-45(13)
C(105)	161(13)	127(10)	130(10)	-41(7)	39(11)	-13(8)
C(106)	89(7)	410(30)	137(12)	-211(17)	2(7)	-39(10)
C(7)	91(3)	104(3)	101(3)	-4(2)	8(2)	-12(2)
C(8)	104(3)	93(3)	125(3)	-7(2)	8(3)	-12(2)
C(9)	88(3)	83(2)	113(3)	-3(2)	2(2)	-9(2)
C(10)	90(4)	125(4)	128(4)	4(3)	-1(3)	-14(3)
C(11)	91(3)	147(5)	155(5)	-3(4)	25(4)	2(3)
C(12)	129(6)	155(5)	125(5)	-2(4)	30(4)	-18(4)
C(13)	134(6)	134(4)	124(4)	14(3)	15(4)	-12(4)
C(14)	99(3)	101(3)	138(4)	17(3)	-3(3)	-6(3)
C(15)	107(3)	118(4)	105(3)	-16(3)	5(3)	-3(3)
C(16)	96(3)	107(3)	127(4)	7(3)	1(3)	-19(3)

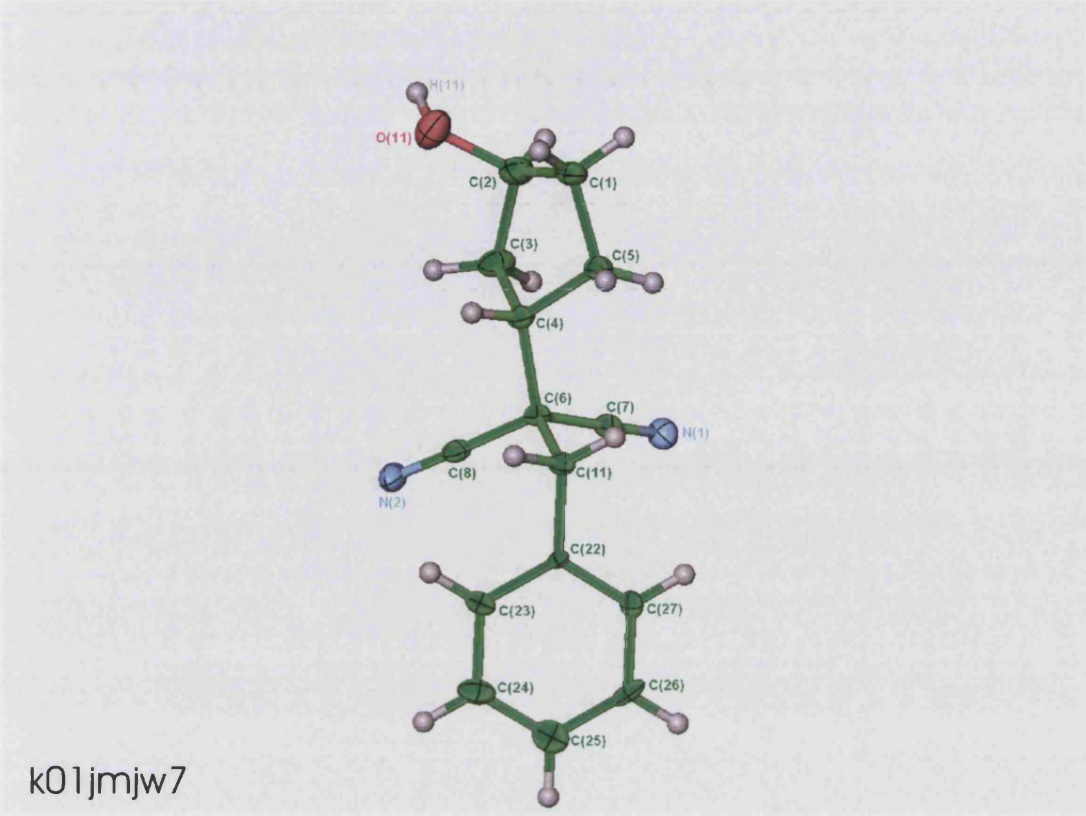
Table 23 Anisotropic displacement parameters ($Å^2$ x 10^3) for k01jmjw3

The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

Atom	x	y	z	U [eq]
H(1)	1008	5573	5087	266
H(101)	-3959	6040	3839	249
H(1A)	1339	6577	3869	125
H(2A)	892	4233	3987	178
H(2B)	-741	4452	3568	178
H(3)	-1291	4331	4961	190
H(4A)	-3023	5821	4217	202
H(4B)	-2608	6633	4950	202
H(5A)	-919	7818	4364	248
H(5B)	-2598	7855	3961	248
H(6A)	-1518	6177	2975	283
H(6B)	-524	7542	2945	283
H(10A)	-340	6557	2969	159
H(10B)	-146	4263	3751	176
H(10C)	-1305	4586	3084	176
H(103)	-2632	4664	4373	193
H(10D)	-2069	6865	4961	179
H(10E)	-512	5989	4948	179
H(10F)	-78	8131	4727	167
H(10G)	-1094	8008	3972	167
H(10H)	1883	7305	3749	255
H(10I)	1562	6049	4280	255
H(8A)	1648	7461	2216	129
H(8B)	3116	7283	2762	129
H(10)	5562	6202	2277	137
H(11)	7184	5783	1231	157
H(12)	6067	5834	30	164
H(13)	3483	6347	-123	157
H(14)	1877	6828	902	136

Table 24 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for k01jmjw3

4.5 trans-2-Benzyl-2-(3-oxo-cyclopentyl)-malononitrile; trans-180



Identification code	k01jmjw7
Empirical formula	$C_{15}H_{16}N_2O$
Formula weight	240.30
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 9.0180(2) Å α = 90 °
	b = 15.8960(4) Å β = 99.1150(10) °
	c = 9.3060(3) Å γ = 90 °
Volume	1317.17(6) $Å^3$
Z	4
Density (calculated)	1.212 Mg m^{-3}
Absorption coefficient	0.077 mm^{-1}
F(000)	512
Crystal size	0.30 x 0.25 x 0.13 mm
Theta range for data collection	3.66 to 27.46 °
Index ranges	-11<=h<=11; -20<=k<=20; -12<=l<=12
Reflections collected	24974
Independent reflections	2988 [R(int) = 0.0584]
Reflections observed (>2σ)	2083
Data Completeness	0.993
Max. and min. transmission	0.9904 and 0.9772
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2988 / 0 / 195
Goodness-of-fit on F^2	1.416
Final R indices [I>2σ(I)]	R_1 = 0.1050 wR_2 = 0.3201
R indices (all data)	R_1 = 0.1366 wR_2 = 0.3545
Largest diff. peak and hole	2.049 and -0.624 $eÅ^{-3}$

Table 25 Crystal data and structure refinement for k01jmjw7

Notes: Xtal quality moderate. Phenyl ring disorder modelled as 2 partial aromatics (rigid hexagons) in ratio 55:45, although disorder more extensive. Hydrogens included at calculated positions throughout, including alcoholic moiety.

Atom	x	y	z	U [eq]
O(11)	2577(3)	5530(2)	-927(4)	69(1)
N(1)	1420(3)	1779(2)	-1965(3)	44(1)
N(2)	-2243(3)	3517(2)	-2931(3)	48(1)
C(1)	3338(4)	4338(2)	552(4)	54(1)
C(2)	3021(4)	4631(3)	-994(5)	59(1)
C(3)	1686(4)	4141(2)	-1721(4)	50(1)
C(4)	973(3)	3761(2)	-475(3)	33(1)
C(5)	2341(3)	3584(2)	695(3)	37(1)
C(6)	-69(3)	2997(2)	-910(3)	29(1)
C(7)	762(3)	2308(2)	-1513(3)	33(1)
C(8)	-1294(3)	3279(2)	-2057(3)	34(1)
C(11)	-726(3)	2656(2)	427(3)	30(1)
C(22)	-1996(9)	2033(6)	30(20)	25(3)
C(23)	-3459(11)	2331(4)	-306(17)	30(2)
C(24)	-4633(8)	1773(5)	-733(11)	48(3)
C(25)	-4344(8)	917(5)	-821(10)	61(4)
C(26)	-2881(9)	619(4)	-481(10)	43(3)
C(27)	-1707(7)	1177(6)	-53(15)	34(2)
C(32)	-1811(9)	1921(5)	35(18)	34(3)
C(33)	-3340(10)	2064(4)	-376(14)	42(2)
C(34)	-4306(7)	1392(5)	-769(9)	56(3)
C(35)	-3742(8)	578(4)	-752(9)	60(3)
C(37)	-2213(8)	435(4)	-342(10)	58(3)
C(38)	-1247(6)	1107(6)	52(16)	40(2)

Table 26 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for k01jmjw7

U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

O(11)-C(2)	1.488(5)	N(1)-C(7)	1.147(4)
N(2)-C(8)	1.147(4)	C(1)-C(2)	1.497(6)
C(1)-C(5)	1.516(4)	C(2)-C(3)	1.503(5)
C(3)-C(4)	1.535(4)	C(4)-C(5)	1.537(4)
C(4)-C(6)	1.549(4)	C(6)-C(7)	1.487(4)
C(6)-C(8)	1.478(4)	C(6)-C(11)	1.558(4)
C(11)-C(22)	1.514(7)	C(11)-C(32)	1.530(6)
C(22)-C(23)	1.3900	C(22)-C(27)	1.3900
C(23)-C(24)	1.3900	C(24)-C(25)	1.3900
C(25)-C(26)	1.3900	C(26)-C(27)	1.3900
C(32)-C(33)	1.3900	C(32)-C(38)	1.3900
C(33)-C(34)	1.3900	C(34)-C(35)	1.3900
C(35)-C(37)	1.3900	C(37)-C(38)	1.3900
C(2)-C(1)-C(5)	107.8(3)	C(1)-C(2)-C(3)	106.8(3)
C(1)-C(2)-O(11)	105.7(3)	C(3)-C(2)-O(11)	108.4(3)
C(2)-C(3)-C(4)	105.4(3)	C(5)-C(4)-C(3)	102.8(2)
C(5)-C(4)-C(6)	115.3(2)	C(3)-C(4)-C(6)	114.9(2)
C(1)-C(5)-C(4)	102.4(2)	C(7)-C(6)-C(8)	108.3(2)
C(7)-C(6)-C(4)	110.8(2)	C(8)-C(6)-C(4)	107.7(2)
C(7)-C(6)-C(11)	108.8(2)	C(8)-C(6)-C(11)	110.3(2)
C(4)-C(6)-C(11)	110.9(2)	N(1)-C(7)-C(6)	179.0(3)
N(2)-C(8)-C(6)	178.3(3)	C(22)-C(11)-C(32)	9.2(7)
C(22)-C(11)-C(6)	113.8(7)	C(32)-C(11)-C(6)	112.6(7)
C(23)-C(22)-C(27)	120.0	C(23)-C(22)-C(11)	119.1(6)
C(27)-C(22)-C(11)	120.8(6)	C(22)-C(23)-C(24)	120.0
C(23)-C(24)-C(25)	120.0	C(24)-C(25)-C(26)	120.0
C(27)-C(26)-C(25)	120.0	C(26)-C(27)-C(22)	120.0
C(33)-C(32)-C(38)	120.0	C(33)-C(32)-C(11)	120.7(6)
C(38)-C(32)-C(11)	119.3(6)	C(34)-C(33)-C(32)	120.0
C(33)-C(34)-C(35)	120.0	C(37)-C(35)-C(34)	120.0
C(35)-C(37)-C(38)	120.0	C(37)-C(38)-C(32)	120.0

Table 27 Bond lengths [Å] and angles [°] for k01jmjw7

Symmetry transformations used to generate equivalent atoms:

Atom	U11	U22	U33	U23	U13	U12
O(11)	81(2)	52(2)	79(2)	11(1)	28(2)	4(1)
N(1)	44(2)	46(2)	43(2)	-10(1)	7(1)	3(1)
N(2)	53(2)	38(2)	47(2)	3(1)	-7(1)	-4(1)
C(1)	43(2)	44(2)	67(2)	10(2)	-12(2)	-13(1)
C(2)	49(2)	58(2)	68(3)	23(2)	3(2)	-14(2)
C(3)	62(2)	50(2)	36(2)	9(1)	2(1)	-22(2)
C(4)	37(2)	27(2)	33(2)	-1(1)	2(1)	-6(1)
C(5)	38(2)	35(2)	34(2)	3(1)	-1(1)	-7(1)
C(6)	29(1)	30(2)	28(1)	-2(1)	3(1)	-5(1)
C(7)	31(1)	38(2)	30(2)	-2(1)	4(1)	-7(1)
C(8)	38(2)	27(2)	35(2)	-1(1)	0(1)	-7(1)
C(11)	31(1)	32(2)	26(1)	-3(1)	4(1)	-5(1)
C(22)	35(7)	17(4)	26(5)	-4(3)	11(5)	-4(4)
C(23)	17(3)	43(5)	30(4)	-12(4)	6(3)	-4(3)
C(24)	25(4)	86(8)	35(4)	-1(5)	10(3)	-7(4)
C(25)	73(8)	76(10)	37(5)	-21(6)	19(5)	-47(8)
C(26)	65(9)	22(4)	48(5)	-11(4)	33(6)	-21(5)
C(27)	34(5)	30(5)	44(5)	-5(4)	29(5)	0(4)
C(32)	19(3)	52(7)	31(5)	-5(5)	6(3)	-5(4)
C(33)	43(5)	54(5)	28(4)	2(4)	5(3)	1(4)
C(34)	24(4)	111(11)	35(4)	0(5)	5(3)	-27(5)
C(35)	62(7)	69(6)	52(5)	-14(4)	24(5)	-47(6)
C(37)	67(7)	45(5)	68(5)	-12(4)	33(5)	-14(4)
C(38)	34(4)	33(4)	55(4)	-4(3)	18(4)	-7(3)

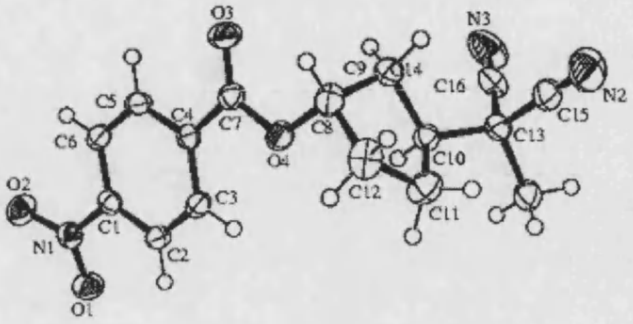
Table 28 Anisotropic displacement parameters ($Å^2$ x 10^3) for k01jmjw7

The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

Atom	x	y	z	U [eq]
H(11)	2781	5785	-1662	83
H(1A)	3121	4793	1215	64
H(1B)	4408	4178	812	64
H(2)	3911	4558	-1501	71
H(3A)	2003	3692	-2344	60
H(3B)	965	4515	-2330	60
H(4)	361	4210	-96	39
H(5A)	2052	3556	1677	44
H(5B)	2844	3052	497	44
H(11A)	109	2469	1180	36
H(11B)	-1260	3117	846	36
H(23)	-3657	2916	-246	36
H(24)	-5633	1977	-966	58
H(25)	-5146	536	-1113	73
H(26)	-2684	34	-541	51
H(27)	-708	974	179	40
H(33)	-3725	2621	-388	50
H(34)	-5351	1489	-1050	67
H(35)	-4402	118	-1021	71
H(37)	-1828	-122	-330	69
H(38)	-202	1009	333	48

Table 29 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for k01jmjw7

4.6 *para*-Nitro-benzoic acid 3-(dicyano-methyl-methyl)-cyclopentyl ester; trans-177



Identification code	h02jmjw3
Empirical formula	$C_{16}H_{15}N_3O_4$
Formula weight	313.31
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 5.87500(10) Å α = 90 °
	b = 7.80100(10) Å β = 94.2240(8) °
	c = 33.5920(7) Å γ = 90 °
Volume	1535.37(5) $Å^3$
Z	4
Density (calculated)	1.355 Mg m^{-3}
Absorption coefficient	0.100 mm^{-1}
F(000)	656
Crystal size	0.45 x 0.25 x 0.08 mm
Colour, shape	Colourless plate
Theta range for data collection	4.04 to 30.06 °
Limiting indices	8<=h<=8, -10<=k<=10, -47<=l<=47
Reflections collected	19898
Independent reflections	4431 [R(int) = 0.1081]
Data Completeness	0.986

Max. and min. transmission	0.9921 and 0.9566
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4431 / 0 / 209
Goodness-of-fit on F^2	0.952
Final R indices [I>2σ(I)]	R1 = 0.0515, wR2 = 0.1014
R indices (all data)	R1 = 0.1487, wR2 = 0.1264
Extinction coefficient	0.007(2)
Largest diff. peak and hole	0.255 and -0.206 $eÅ^{-3}$

Table 30 Crystal data and structure refinement for h02jmjw3

Atom	x	y	z	U [eq]
O(1)	-4410(2)	5471(2)	-609(1)	43(1)
O(2)	-2581(2)	7152(2)	-986(1)	43(1)
N(1)	-2895(2)	6525(2)	-661(1)	30(1)
C(1)	-1376(3)	7048(2)	-316(1)	26(1)
C(2)	-2023(3)	6720(2)	62(1)	28(1)
C(3)	-589(3)	7238(2)	386(1)	28(1)
C(4)	1465(3)	8058(2)	325(1)	25(1)
C(5)	2079(3)	8348(2)	-62(1)	27(1)
C(6)	654(3)	7852(2)	-388(1)	28(1)
O(3)	4834(2)	9373(2)	621(1)	40(1)
O(4)	2231(2)	8357(1)	1019(1)	33(1)
C(7)	3034(3)	8669(2)	661(1)	28(1)
C(8)	3672(3)	8865(2)	1373(1)	35(1)
C(9)	5341(3)	7438(2)	1483(1)	36(1)
C(10)	3801(3)	6047(2)	1639(1)	28(1)
C(11)	2008(3)	7039(2)	1860(1)	41(1)
C(12)	2122(3)	8903(2)	1715(1)	43(1)
C(13)	5011(3)	4612(2)	1890(1)	29(1)
C(14)	3266(3)	3290(2)	2022(1)	37(1)
N(2)	7202(3)	5908(3)	2528(1)	68(1)
C(15)	6277(3)	5337(2)	2250(1)	40(1)
N(3)	7949(3)	3062(2)	1467(1)	65(1)
C(16)	6678(3)	3734(2)	1654(1)	39(1)

Table 31 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for h02jmjw3

U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

O(1)-N(1)	1.2337(16)
O(2)-N(1)	1.2225(16)
N(1)-C(1)	1.468(2)
C(1)-C(2)	1.376(2)
C(1)-C(6)	1.385(2)
C(2)-C(3)	1.384(2)
C(3)-C(4)	1.394(2)
C(4)-C(5)	1.393(2)
C(4)-C(7)	1.482(2)
C(5)-C(6)	1.386(2)
O(3)-C(7)	1.2078(18)
O(4)-C(7)	1.3434(19)
O(4)-C(8)	1.4639(19)
C(8)-C(9)	1.512(2)
C(8)-C(12)	1.518(2)
C(9)-C(10)	1.530(2)
C(10)-C(11)	1.541(2)
C(10)-C(13)	1.544(2)
C(11)-C(12)	1.536(2)
C(13)-C(16)	1.475(2)
C(13)-C(15)	1.482(2)
C(13)-C(14)	1.542(2)
N(2)-C(15)	1.139(2)
N(3)-C(16)	1.139(2)

Table 32 Bond lengths [Å] for h02jmjw3

O(2)-N(1)-O(1)	123.42(14)	O(2)-N(1)-C(1)	118.15(13)
O(1)-N(1)-C(1)	118.43(14)	C(2)-C(1)-C(6)	123.15(15)
C(2)-C(1)-N(1)	118.98(14)	C(6)-C(1)-N(1)	117.88(14)
C(1)-C(2)-C(3)	118.44(14)	C(2)-C(3)-C(4)	120.23(15)
C(5)-C(4)-C(3)	119.74(15)	C(5)-C(4)-C(7)	118.00(14)
C(3)-C(4)-C(7)	122.26(14)	C(6)-C(5)-C(4)	120.76(14)
C(1)-C(6)-C(5)	117.68(15)	C(7)-O(4)-C(8)	117.20(12)
O(3)-C(7)-C(4)	123.37(15)	O(3)-C(7)-C(4)	124.17(15)
O(4)-C(7)-C(4)	112.46(13)	O(4)-C(8)-C(9)	108.99(13)
O(4)-C(8)-C(12)	106.12(13)	C(9)-C(8)-C(12)	104.08(14)
C(8)-C(9)-C(10)	102.52(13)	C(9)-C(10)-C(11)	104.57(13)
C(9)-C(10)-C(13)	116.20(13)	C(11)-C(10)-C(13)	113.82(14)
C(12)-C(11)-C(10)	105.95(13)	C(8)-C(12)-C(11)	105.35(14)
C(16)-C(13)-C(15)	107.59(14)	C(16)-C(13)-C(14)	109.05(14)
C(15)-C(13)-C(14)	109.01(14)	C(16)-C(13)-C(10)	109.83(14)
C(15)-C(13)-C(10)	110.60(13)	C(14)-C(13)-C(10)	110.68(12)
N(2)-C(15)-C(13)	178.4(2)	N(3)-C(16)-C(13)	179.1(2)

Table 33 Bond angles [°] for h02jmjw3

Symmetry transformations used to generate equivalent atoms:

Atom	U11	U22	U33	U23	U13	U12
O(1)	37(1)	47(1)	45(1)	1(1)	-1(1)	-15(1)
O(2)	50(1)	50(1)	27(1)	2(1)	2(1)	-10(1)
N(1)	30(1)	30(1)	32(1)	-1(1)	3(1)	2(1)
C(1)	24(1)	22(1)	30(1)	-1(1)	-1(1)	2(1)
C(2)	25(1)	28(1)	32(1)	4(1)	5(1)	-2(1)
C(3)	31(1)	28(1)	27(1)	4(1)	6(1)	0(1)
C(4)	26(1)	21(1)	30(1)	3(1)	4(1)	3(1)
C(5)	22(1)	25(1)	35(1)	3(1)	4(1)	-1(1)
C(6)	30(1)	25(1)	30(1)	5(1)	8(1)	1(1)
O(3)	34(1)	50(1)	37(1)	2(1)	2(1)	-15(1)
O(4)	36(1)	34(1)	28(1)	4(1)	0(1)	-7(1)
C(7)	30(1)	24(1)	31(1)	3(1)	4(1)	0(1)
C(8)	44(1)	29(1)	32(1)	1(1)	-5(1)	-10(1)
C(9)	32(1)	44(1)	31(1)	3(1)	-2(1)	-9(1)
C(10)	30(1)	29(1)	26(1)	1(1)	0(1)	-2(1)
C(11)	44(1)	35(1)	45(1)	1(1)	15(1)	3(1)
C(12)	58(1)	33(1)	37(1)	-5(1)	3(1)	5(1)
C(13)	27(1)	34(1)	26(1)	-1(1)	-2(1)	-4(1)
C(14)	39(1)	34(1)	38(1)	7(1)	-4(1)	-6(1)
N(2)	80(1)	82(1)	41(1)	-3(1)	-16(1)	-28(1)
C(15)	42(1)	45(1)	31(1)	3(1)	-5(1)	-10(1)
N(3)	43(1)	85(1)	64(1)	-13(1)	-3(1)	22(1)
C(16)	30(1)	46(1)	40(1)	0(1)	-7(1)	4(1)

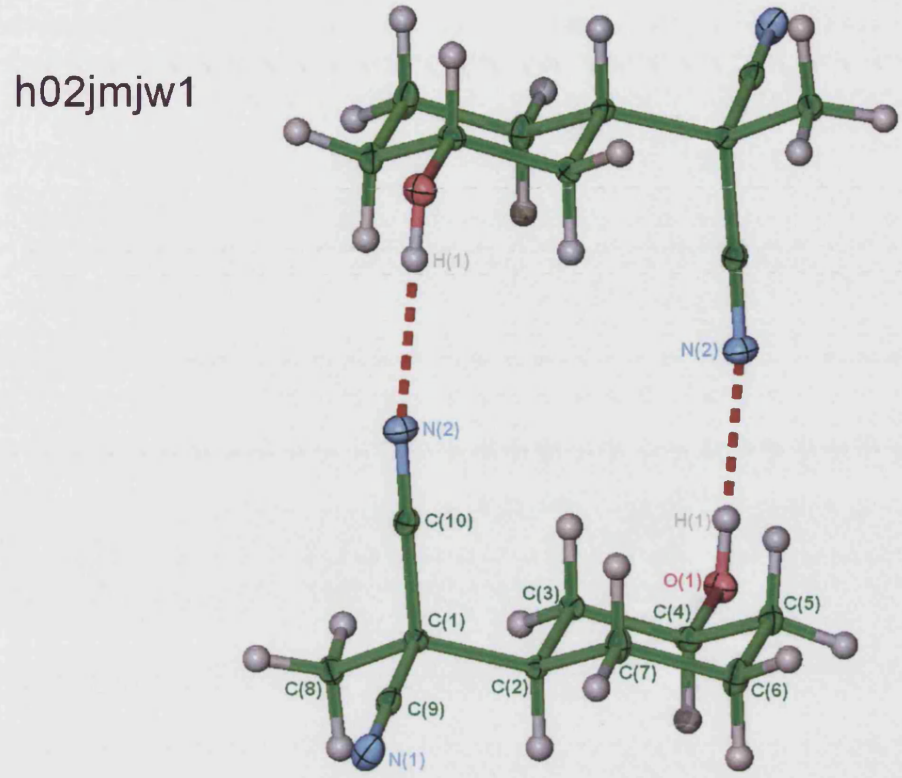
Table 34 Anisotropic displacement parameters ($Å^2$ x 10^3) for h02jmjw3

The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

Atom	x	y	z	U [eq]
H(2)	-3420	6152	101	33
H(3)	-1007	7034	649	34
H(5)	3490	8892	-102	33
H(6)	1056	8055	-653	34
H(8)	4451	9988	1337	42
H(9A)	6513	7809	1692	43
H(9B)	6105	7034	1247	43
H(10)	2982	5491	1402	34
H(11A)	466	6557	1796	49
H(11B)	2365	6976	2153	49
H(12A)	583	9323	1622	51
H(12B)	2760	9659	1932	51
H(14A)	2411	2814	1786	56
H(14B)	2207	3852	2193	56
H(14C)	4071	2365	2171	56

Table 35 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for h02jmjw3

4.7 cis-2-(3-Hydroxy-cyclohexyl)-2-methyl-malononitrile; cis-168



Identification code	k02jmjw1
Empirical formula	$C_{10}H_{14}N_2O$
Formula weight	178.23
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 7.06600(10) Å α = 90 °
	b = 16.7090(3) Å β = 94.7460(10) °
	c = 8.5650(2) Å γ = 90 °
Volume	1007.77(3) $Å^3$
Z	4
Density (calculated)	1.175 Mg m^{-3}
Absorption coefficient	0.078 mm^{-1}
F(000)	384
Crystal size	0.50 x 0.25 x 0.08 mm
Theta range for data collection	3.60 to 27.51 °
Index ranges	-8<=h<=9; -21<=k<=21; -11<=l<=11
Reflections collected	18892
Independent reflections	2304 [R(int) = 0.0650]
Reflections observed (>2σ)	1833
Data Completeness	0.996
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.05 and 0.82
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2304 / 0 / 121
Goodness-of-fit on F^2	0.994
Final R indices [I>2σ(I)]	R_1 = 0.0421 wR_2 = 0.1094
R indices (all data)	R_1 = 0.0591 wR_2 = 0.1190
Largest diff. peak and hole	0.287 and -0.246 $eÅ^{-3}$

Table 36 Crystal data and structure refinement for k02jmjw1

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O1-H1	0.840	2.162	172.92	2.997	N2 [-x+1, -y, -z+1]

Atom	x	y	z	U [eq]
O(1)	3663(1)	2177(1)	5413(1)	33(1)
N(1)	11392(2)	781(1)	1101(2)	39(1)
N(2)	7019(2)	-644(1)	2904(2)	34(1)
C(1)	7864(2)	779(1)	1866(1)	21(1)
C(2)	7699(2)	1407(1)	3200(1)	21(1)
C(3)	5679(2)	1458(1)	3719(2)	22(1)
C(4)	5548(2)	2106(1)	4966(2)	25(1)
C(5)	6964(2)	1959(1)	6365(2)	29(1)
C(6)	8978(2)	1893(1)	5863(2)	35(1)
C(7)	9122(2)	1247(1)	4614(2)	30(1)
C(8)	6561(2)	967(1)	372(2)	26(1)
C(9)	9866(2)	766(1)	1443(2)	26(1)
C(10)	7415(2)	-30(1)	2442(2)	23(1)

Table 37 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for k02jmjw1

U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

O(1)-C(4)	1.4213(15)	N(1)-C(9)	1.1407(17)
N(2)-C(10)	1.1430(17)	C(1)-C(10)	1.4818(17)
C(1)-C(9)	1.4894(17)	C(1)-C(8)	1.5453(17)
C(1)-C(2)	1.5624(16)	C(2)-C(3)	1.5321(16)
C(2)-C(7)	1.5330(18)	C(3)-C(4)	1.5298(17)
C(4)-C(5)	1.5163(19)	C(5)-C(6)	1.5242(19)
C(6)-C(7)	1.5284(19)		
C(10)-C(1)-C(9)	107.58(10)	C(10)-C(1)-C(8)	109.39(10)
C(9)-C(1)-C(8)	108.30(10)	C(10)-C(1)-C(2)	109.76(10)
C(9)-C(1)-C(2)	108.49(9)	C(8)-C(1)-C(2)	113.16(10)
C(3)-C(2)-C(7)	110.26(10)	C(3)-C(2)-C(1)	112.15(10)
C(7)-C(2)-C(1)	112.16(10)	C(4)-C(3)-C(2)	110.68(10)
O(1)-C(4)-C(5)	111.86(10)	O(1)-C(4)-C(3)	111.00(10)
C(5)-C(4)-C(3)	111.25(10)	C(4)-C(5)-C(6)	111.03(11)
C(5)-C(6)-C(7)	111.49(11)	C(6)-C(7)-C(2)	110.64(11)
N(1)-C(9)-C(1)	177.86(14)	N(2)-C(10)-C(1)	177.85(14)

Table 38 Bond lengths [Å] and angles [°] for k02jmjw1

Symmetry transformations used to generate equivalent atoms:

Atom	U11	U22	U33	U23	U13	U12
O(1)	31(1)	31(1)	37(1)	0(1)	10(1)	6(1)
N(1)	29(1)	42(1)	47(1)	-14(1)	12(1)	-4(1)
N(2)	36(1)	28(1)	39(1)	4(1)	2(1)	-2(1)
C(1)	20(1)	22(1)	22(1)	-2(1)	5(1)	-1(1)
C(2)	23(1)	21(1)	21(1)	-2(1)	4(1)	-2(1)
C(3)	21(1)	23(1)	22(1)	1(1)	3(1)	1(1)
C(4)	28(1)	22(1)	25(1)	0(1)	8(1)	2(1)
C(5)	34(1)	32(1)	23(1)	-6(1)	4(1)	-1(1)
C(6)	29(1)	45(1)	31(1)	-15(1)	-1(1)	-3(1)
C(7)	23(1)	40(1)	27(1)	-9(1)	-1(1)	1(1)
C(8)	31(1)	27(1)	21(1)	0(1)	2(1)	1(1)
C(9)	27(1)	25(1)	27(1)	-7(1)	5(1)	-2(1)
C(10)	21(1)	25(1)	23(1)	-3(1)	1(1)	0(1)

Table 39 Anisotropic displacement parameters ($Å^2$ x 10^3) for k02jmjw1

The anisotropic displacement factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	x	y	z	U [eq]
H(1)	3368	1758	5878	39
H(2)	8011	1942	2767	26
H(3A)	4779	1581	2803	26
H(3B)	5318	934	4149	26
H(4)	5888	2627	4487	30
H(5A)	6629	1458	6895	35
H(5B)	6901	2404	7121	35
H(6A)	9860	1764	6787	42
H(6B)	9364	2415	5442	42
H(7A)	8864	717	5065	36
H(7B)	10427	1240	4272	36
H(8A)	6819	587	-455	39
H(8B)	6808	1513	23	39
H(8C)	5230	920	602	39

Table 40 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for k02jmjw1

4.8 References

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Chapter 5

5.0 Experimental

5.1 General Experimental

Reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen. Apparatus, needles and syringes were oven-dried and cooled. General solvents were distilled before use. Anhydrous toluene and hexane were distilled from sodium wire. Diethyl ether and THF were distilled from the anion of benzophenonketal radical. Dichloromethane, petroleum ether (boiling point 40-60 °C) and acetonitrile were distilled from CaH_2. Ethyl acetate was distilled from K_2CO_3. All solvents used were stored in the presence of activated 3 Å molecular sieves. Acetone, cyclohexane, DCE, DMF, isopropanol and methanol were all purchased in anhydrous form from commercially available suppliers.

TLC using commercially available plastic-backed plates coated with Merck Kieselgel 60 GF_{254} neutral (Type E) silica monitored all reactions. Visualisation of these plates was by 254 nm light or with $KMnO_4$/Vanillin dips followed by heating. Organic layers were dried with anhydrous Na_2SO_4 or $MgSO_4$ and evaporated with a Büchii rotary evaporator. Further evaporation was carried out on a high-vacuum line where necessary. Chromatographic purification of products was accomplished using forced-flow chromatography and silica gel (0.04-0.063 nm) pore diameter *ca.* 6 nm, obtained from Fisher according to the procedure of Still.[1]

Melting points were recorded on a Büchii 535 Series instrument and are uncorrected.

IR spectra were recorded as thin films; solutions ($CDCl_3$) or KBr discs using a Perkin-Elmer 1600 Series FT-IR spectrophotometer in the range 4000-600 cm^{-1}, with internal background scan. Absorption maxima are recorded in wavenumbers (cm^{-1}) and classified as strong (s), medium (m), weak (w) or broad (br).

Proton (δ ^1H) NMR spectra were run in $CDCl_3$ using either a Bruker AM-300 (300 MHz), Jeol (270 MHz), or Jeol (400 MHz) instrument. Chemical shifts are reported relative to Me_4Si (δ 0.00 ppm) as internal standard. Coupling constants (*J*) are given Hz and multiplicities denoted as singlet (s), doublet (d), triplet (t), multiplet (m), or broad (br). Carbon-13 (δ ^{13}C) NMR spectra were run in $CDCl_3$ and were recorded using a Bruker WH-400 (100 MHz) or a Bruker AM-300 (75 MHz).

Mass spectra, including high-resolution spectra, were recorded on a Micromass Autospec Spectrometer using electron impact (EI+) ionisation, chemical impact (CI+, *iso*-butane) ionisation, and/or Fast Atom Bombardment (FAB+) ionisation.

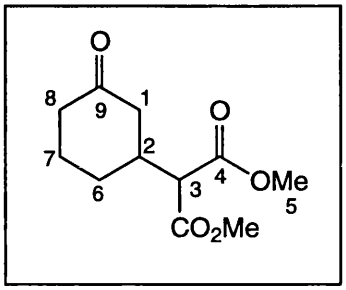
Elemental analyses were performed using a Carlo Erba 1106 Elemental Analyser or an Exeter Analytical Inc. CE-440 Elemental Analyser.

HPLC was performed using SP ThermoSeparation SpectraSERIES and Spectra-Physics spectrometer, SP4290 Integrator, SP8700 Solvent Delivery System and Spectra 100 Variable Wavelength Detector. All separations were performed using a Chiracel OB column (25 cm) obtained from Fisher Scientific.

Unless preparative details are provided all chemicals were commercially available and purchased from Acros, Fluka, Lancaster or Sigma-Aldrich.

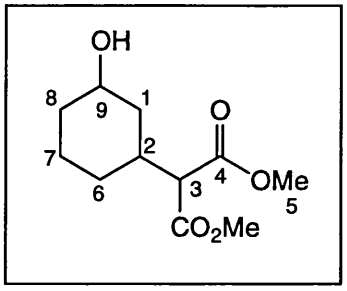
5.2 Experimental Procedures: Chapter 2.0 Experimental

Preparation of 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester 115[2,3]



2-Cyclohexen-1-one **113** (4.766 g, 50 mmol) in methanol (5 mL) was added dropwise to a methanolic (25 mL) suspension of sodium hydride (0.120 g, 5.0 mmol) and dimethyl malonate **114** (6.87 g, 50 mmol) at 0 °C. After 4.5 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (100 mL) and washed with water (3 x 100 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by distillation under reduced pressure gave **115** as a colourless oil (8.51 g, 75%). **115**: b.p. 135-137 °C at 1-2 mm Hg; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.49 (dddd, *J* = 2, 12, 12, 12 Hz, 1H), 1.69 (app dtq, *J* = 1, 4, 12 Hz, 1H), 1.91-1.99 (m, 1H), 2.03-2.12 (m, 1H), 2.21-2.32 (m, 2H), 2.36-2.47 (m, 2H), 2.48-2.59 (m, 1H), 3.36 (d, *J* = 8 Hz, 1H, **H**$_3$), 3.75 (s, 3H, **H**$_5$), 3.76 (s, 3H, **H**$_5$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.9, 29.2, 38.5, 41.4, 45.5, 53.0 (**C**$_5$), 57.0 (**C**$_3$), 168.5 (**C**$_4$), 168.6 (**C**$_4$), 209.9 (**C**$_9$); IR ($CHCl_3$): ν (cm^{-1}) = 1737 (C=O), 1710 (C=O); MS (EI+, 70 eV): *m/z* (%) 228 (30) [M^{+}]; HRMS (EI+, 70 eV): $C_{11}H_{16}O_5$ requires 228.0998, found 228.0991; CHN analysis: $C_{11}H_{16}O_5$ requires C 57.89%, H 7.07%, found C 57.00%, H 7.07%.

Preparation of cis/trans-2-(3-hydroxy-cyclohexyl)-malonic acid dimethyl ester cis/trans-138



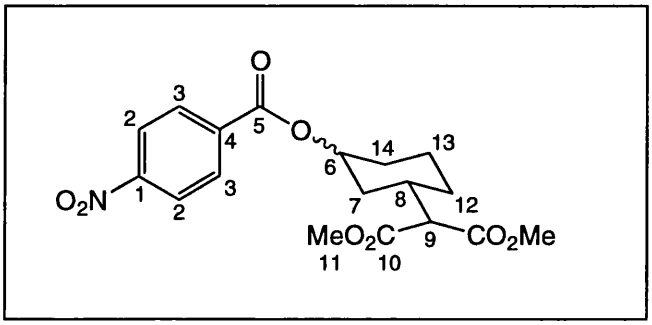
2-(3-Oxo-cyclohexyl)-malonic acid dimethyl ester **115** (2.283 g, 10 mmol) in anhydrous methanol (15 mL) was cooled to 0 °C whilst sodium borohydride (0.560 g,

15 mmol) was added portionwise over 0.1 hours. After 0.5 hours, the reaction was quenched with distilled water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Purification by flash-column chromatography (SiO_2, 3:1 petroleum ether/diethyl ether) gave cis/trans-**138** as a colourless oil (2.140 g, 93%, 80:20 cis/trans). cis/trans-**138**: ^{1}H NMR (400 MHz, $CHCl_3$, 25 °C): δ = 0.84-1.17 (m, 2H), 1.19-1.33 (m, 1H), 1.34-1.51 (m, 1H), 1.54-1.80 (m, 2H), 1.86-1.96 (m, 1H), 2.20-2.30 (m, 1H), 2.44-2.54 (m, 1H), 3.16 (d, *J* = 9 Hz, 1H, H_3), 3.17 (d, *J* = 9 Hz, 1H, H_3), 3.51-3.59 (m, 1H, H_{9ax}), 3.56 (s, 3H, H_5), 3.60 (s, 3H, H_5), 4.09 (br s, 1H, H_{9eq}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.1, 23.9, 29.8, 30.2, 32.6, 32.8, 35.5, 36.8, 37.3, 40.0, 52.8 (C_5), 52.8 (C_5), 57.5 (C_3), 57.9 (C_3), 66.4 (C_9), 70.5 (C_9), 169.3 (C_4), 169.4 (C_4); IR ($CHCl_3$): ν (cm^{-1}) = 3486 (O-H), 1750 (C=O); MS (EI+, 70 eV): *m/z* (%) 212 (100) [M^{+}-H_2O]; MS (CI+): 231 [MH^+]; HRMS (EI+, 70 eV): $C_{11}H_{18}O_5$ requires 230.1154, found 230.1161.

Control reaction for the preparation of 2-(3-hydroxy-cyclohexyl)-malonic acid dimethyl ester 138

Into an anhydrous methanolic solution (2 mL) of sodium methoxide (0.054 g, 1.0 mmol) and dimethyl malonate **114** (0.132 g, 1.0 mmol) was added 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) in anhydrous methanol (3 mL). After 264 hours, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL), and washed with water (2 x 50 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (0.230 g, 100% recovery, 0% conversion into **138** determined by ^{1}H NMR).

Preparation of cis/trans-2-[3-(4-nitro-benzoyloxy)-cyclohexyl]-malonic acid dimethyl ester 139



para-Nitrobenzoyl chloride **176** (0.338 g, 1.82 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of **138** (0.419 g, 1.82 mmol), Et_3N (0.28 mL, 2.00 mmol) and DMAP (0.022 g, 0.18 mmol) in dichloromethane (15 mL). After 4 hours at room temperature, the reaction was quenched with $NaHCO_3$ (30 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash-column chromatography (SiO_2, 3:1 petroleum ether/diethyl ether) gave cis/trans-**139** as a white solid (0.642 g, 93%, 80:20 cis/trans). cis/trans-**139**: ^1H NMR (400 MHz, $CHCl_3$, 25 °C): δ = 1.02-1.22 (m, 2H), 1.37-1.58 (m, 2H), 1.62-1.90 (m, 2H), 1.92-2.14 (m, 2H), 2.20-2.30 (m, 1H), 2.49-2.58 (m, 1H), 3.21 (d, *J* = 8 Hz, 1H, $\mathbf{H_9}$), 3.26 (d, *J* = 8 Hz, 1H, $\mathbf{H_9}$), 3.21 (s, 3H, $\mathbf{H_{11}}$), 3.27 (s, 3H, **H11**), 4.93-5.00 (m, 1H, $\mathbf{H_{6ax}}$), 5.34-5.35 (br s, 1H, $\mathbf{H_{6eq}}$) 8.11-8.26 (m, 4H, Ar-**H**); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.8, 23.5, 29.5, 29.8, 31.6, 33.2, 34.2, 35.8, 36.5, 37.3, 40.0, 52.7 ($\mathbf{C_{11}}$), 52.7 ($\mathbf{C_{11}}$), 57.3 ($\mathbf{C_9}$), 57.3 ($\mathbf{C_9}$), 71.6 ($\mathbf{C_6}$), 74.4 ($\mathbf{C_6}$), 123.7 ($\mathbf{C_3}$), 123.8 ($\mathbf{C_3}$), 131.0 ($\mathbf{C_2}$), 131.0 ($\mathbf{C_2}$), 136.3 ($\mathbf{C_4}$), 136.4 ($\mathbf{C_4}$), 150.7 ($\mathbf{C_1}$), 150.7 ($\mathbf{C_1}$), 164.1 ($\mathbf{C_5}$), 169.0 ($\mathbf{C_{10}}$), 169.0 ($\mathbf{C_{10}}$); MS (CI+): *m/z* 380 [MH^+]; (FAB+): *m/z* 380 [MH^+]; HRMS (FAB+): $C_{18}H_{21}NO_8$ requires 380.1345, found 380.1342.

Control reaction for the preparation of 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester 115 in the presence of 2-cyclohexen-1-ol 112

Into an anhydrous methanolic solution (2 mL) of sodium hydride (0.002 g, 0.1 mmol) and dimethyl malonate **114** (0.132 g, 1.0 mmol) was added 2-cyclohexen-1-one **113** (0.096 g, 1.0 mmol) and 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) in methanol (3 mL). After 6 hours, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2 x 50 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (0.390 g, 100% recovery, 80% **115**; 0% conversion into **138** determined by ^1H NMR).

General Procedure for the aluminium isopropoxide catalysed oxidation of 2-cyclohexen-1-ol 112 by anhydrous acetone

2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol), and aluminium isopropoxide (0.204 g, 1.0 mmol) were added to a 25 mL round-bottom flask fitted with a condenser and

containing anhydrous acetone (10 mL). After 18 hours at 56 °C under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (95% conversion into **113** determined by ^1H NMR).

General Procedure for the aluminium isopropoxide catalysed oxidation of 2-cyclohexen-1-ol 112 by 2-butanone

2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-butanone (0.144 g, 2.0 mmol) in anhydrous toluene (8 mL) was heated to 110 °C into which aluminium isopropoxide (0.051 g, 0.25 mmol) in anhydrous toluene (2 mL) was added dropwise. After 2.5 hours at 56 °C under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil (92% conversion into **113** determined by ^1H NMR).

Aluminium isopropoxide catalysed reduction of 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester 115 by isopropanol

2-(3-Oxo-cyclohexyl)-malonic acid dimethyl ester **115** (0.228 g, 1.0 mmol) in anhydrous isopropanol (8 mL) was heated to 82 °C and aluminium isopropoxide (0.102 g, 0.5 mmol) in isopropanol (2 mL) was added dropwise. After 18 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **138** as a yellow oil (82% conversion into **138** determined by ^1H NMR).

Aluminium catalysed domino Oppenauer/Michael addition reaction

Under a nitrogen atmosphere, a suspension of sodium hydride (0.024g, 1.0 mmol) and dimethyl malonate **114** (0.132 g, 1.0 mmol) in anhydrous acetone (2 mL) were added to an acetone (8 mL) solution of 2-cyclohexen-1-ol **113** (0.098 g, 1.0 mmol) and aluminium isopropoxide (0.204 g, 1.0 mmol) at 60 °C. After 18 hours the

reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **138** as a pale yellow oil (0.018 g, 8%).

General Procedure for the aluminium isopropoxide catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol 112 and 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester 115

Aluminium isopropoxide (0.204 g, 1.0 mmol) in DCE (2 mL) was added dropwise over a period of 30 minutes to a stirred solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester **115** (0.228 g, 1.0 mmol) in DCE (8 mL) at 82 °C under nitrogen. After 18 hours, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **113/138** as a yellow oil (0.326 g, 100% recovery, 86% conversion determined by ^1H NMR).

Aluminium isopropoxide catalysed transesterification of 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester 115

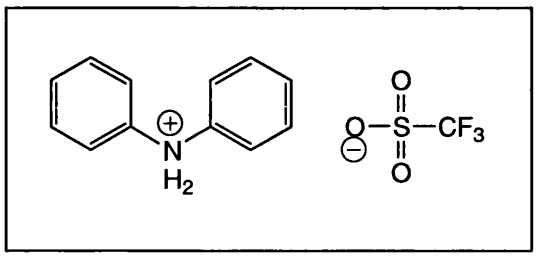
2-(3-Oxo-cyclohexyl)-malonic acid dimethyl ester **115** (0.228 g, 1.0 mmol) and aluminium isopropoxide (0.204 g, 0.5 mmol) were heated to 82 °C in DCE (10 mL). After 5 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **140/141** as a yellow oil (30% conversion determined by ^1H NMR).

Aluminium isopropoxide catalysed transesterification of dimethyl malonate 114

Dimethyl malonate **114** (0.132 g, 1.0 mmol) and aluminium isopropoxide (0.204 g, 1.0 mmol) were heated to 62 °C in THF (8 mL). After 6 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v

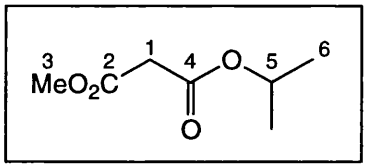
aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give **142/143** as a yellow oil (90% conversion determined by ^1H NMR).

Preparation of diphenylammonium triflate (DPAT)[4]



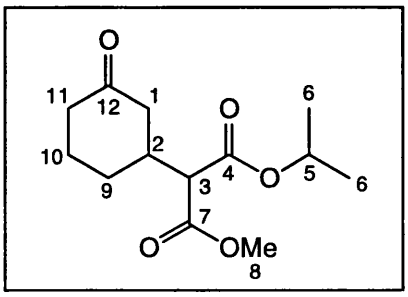
To a stirred solution of diphenylamine (1.127 g, 6.66 mmol) in anhydrous toluene (10 mL) was added dropwise triflic acid (1.00 g, 6.66 mmol). Upon completion of the addition, further anhydrous toluene (3 mL) was added and the mixture allowed to stir for 30 minutes at room temperature. The toluene was removed *in vacuo* and the remaining residue triturated with hexane (50 mL). The white powder thus obtained was collected by filtration and washed with further hexane (3 x 15 mL). Drying under vacuum afforded DPAT as a colourless powder (2.120 g, 99%). **DPAT**: m.p. 132-134 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.37-7.88 (m, Ph); IR (KBr): ν (cm^{-1}) = 3179 (s, N-H), 3022 (m, C_{Ar}-H), 1596 (m, C_{Ar}-C_{Ar}), 1401 (s, SO_2CF_3), 1157 (s, SO_2CF_3), 765 (s, Ph), 693 cm^{-1} (s, Ph).

Preparation of *iso*-propylmethylmalonate 143



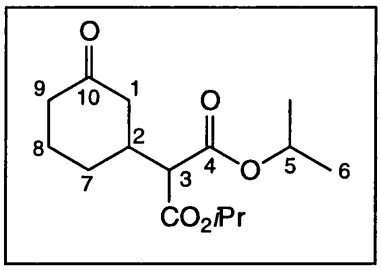
Dimethyl malonate **114** (1.73 mL, 15.14 mmol), isopropanol (0.64 mL, 7.57 mmol), DPAT (0.483 g, 1.51 mmol) and TMSCl (0.19 mL, 1.51 mmol) were heated to 110 °C in anhydrous toluene. After 15 hours, the reaction was cooled, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20:1 petroleum ether/diethyl ether) to give **143** as a colourless oil (0.442 g, 20%). **143**: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.19 (d, J = 6 Hz, 6H, $\mathbf{H_6}$), 3.28 (s, 2H, $\mathbf{H_1}$), 3.67 (s, 3H, $\mathbf{H_3}$), 4.99 (sep, J = 2 Hz, 1 H, $\mathbf{H_5}$).

Preparation of (R/S)-2-(3-oxo-cyclohexyl)-malonic acid *iso*-propyl ester methyl ester 140



2-Cyclohexen-1-one **113** (0.265 g, 2.76 mmol) in THF (2 mL) was added dropwise to a suspension of sodium *tert*-butoxide (0.025 g, 0.28 mmol) and *iso*-propylmethylmalonate **143** (0.442 g, 2.76 mmol) in THF (10 mL). After 6 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave (R/S)-**140** as a colourless oil (0.597 g, 84%). (R/S)-**140**: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.02 (d, J = 6 Hz, 6H, $\mathbf{H_6}$), 1.29 (dddd, J = 2, 12, 12, 12 Hz, 1H), 1.47 (app dtq, J = 1, 4,12 Hz, 1H), 1.65-1.79 (m, 1H), 1.80-1.92 (m, 1H), 1.96-2.12 (m, 2H), 2.13-2.38 (m, 3H), 3.06 (d, 1H, J = 8 Hz, $\mathbf{H_3}$), 3.51 (s, 3H, $\mathbf{H_8}$), 4.85 (sep, J = 2 Hz, 1H, $\mathbf{H_5}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.9 ($\mathbf{C_6}$), 22.1 ($\mathbf{C_6}$), 24.9, 29.1, 29.2, 38.4, 41.4, 45.4, 45.5, 52.8 ($\mathbf{C_8}$), 57.3 ($\mathbf{C_3}$), 57.3 ($\mathbf{C_3}$), 69.7 ($\mathbf{C_5}$), 167.6 ($\mathbf{C_4}$), 167.7 ($\mathbf{C_4}$), 168.7 ($\mathbf{C_7}$), 168.8 ($\mathbf{C_7}$), 210.0 ($\mathbf{C_{12}}$), 210.0 ($\mathbf{C_{12}}$); MS (EI+, 70 eV): *m/z* (%) 256 (23) [M^{+}]; HRMS (EI+, 70 eV): $C_{13}H_{20}O_5$ requires 256.1311, found 256.1314.

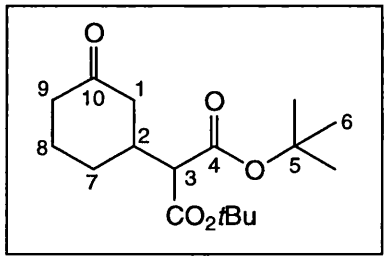
Preparation of 2-(3-oxo-cyclohexyl)-malonic acid di-*iso*-propyl ester 141[3]



2-Cyclohexen-1-one **113** (0.192 g, 2.0 mmol) in THF (2 mL) was added dropwise to a suspension of sodium *tert*-butoxide (0.019 g, 0.2 mmol) and di-*iso*-propyl malonate **142** (0.376 g, 2.0 mmol) in THF (10 mL). After 6 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (25 mL). The aqueous phase was separated and extracted with

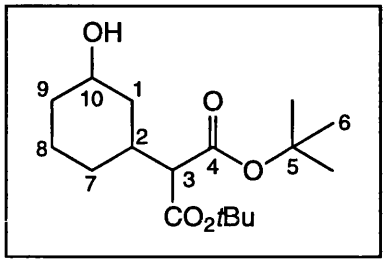
diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **141** as a colourless oil (0.491 g, 86%). **141**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.13 (d, *J* = 6 Hz, 6H, **H**$_6$), 1.14 (d, *J* = 6 Hz, 6H), 1.40 (dddd, *J* = 2, 12, 12, 12 Hz, 1 Hz), 1.56 (app dtq, *J* = 1, 4,12 Hz, 1H), 1.80-1.89 (m, 1H), 1.91-1.99 (m, 1H), 2.09-2.20 (m, 2H), 2.22-2.32 (m, 2H), 2.33-2.44 (m, 1H), 3.11 (d, 1H, *J* = 8 Hz, 1H, **H**$_3$), 4.93 (sep, *J* = 2 Hz, 1H, **H**$_5$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.9, 24.5, 27.9, 38.2, 41.3, 45.3, 57.4 (**C**$_3$), 69.3 (**C**$_5$), 167.6 (**C**$_4$), 167.7 (**C**$_4$), 209.9 (**C**$_{10}$); MS (EI+, 70 eV): *m/z* (%) 284 (47) [M^{+}]; HRMS (EI+, 70 eV): $C_{15}H_{24}O_5$ requires 284.1624, found 284.1629.

Preparation of 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester 144



2-Cyclohexen-1-one **113** (1.000 g, 10 mmol) in THF (2 mL) was added dropwise to a suspension of sodium hydride (0.025 g, 1.0 mmol) and di-*tert*-butyl malonate **146** (2.250 g, 10 mmol) in THF (10 mL). After 6 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (100 mL) and washed with water (2 x 50 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 4:1 petroleum ether/ethyl acetate) gave **144** as a white crystalline solid (3.052 g, 94%). **141**: m.p. 67-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.42 (br s, 9H, **H**$_6$), 1.42-1.75 (m, 2H), 1.94-2.03 (m, 1H), 2.04-2.12 (m, 1H), 2.20-2.32 (m, 2H), 2.36-2.50 (m, 3H), 3.09 (d, *J* = 8 Hz, 1H, **H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 24.7, 28.0 (**C**$_6$), 28.0 (**C**$_6$), 37.9, 41.2, 45.2, 58.8 (**C**$_3$), 81.8 (**C**$_5$), 81.8 (**C**$_5$), 167.0 (**C**$_4$), 209.7 (**C**$_{10}$); IR ($CHCl_3$): ν (cm^{-1}) = 1740 (C=O), 1724 (C=O); MS (FAB+): *m/z* 313 [M^{+}]; HRMS (FAB+): $C_{17}H_{28}O_5$ requires 313.2015, found 313.2028; CHN analysis: $C_{17}H_{28}O_5$ requires C 65.36%, H 9.03%, found C 65.60%, H 9.05%.

Preparation of cis/trans-2-(3-hydroxy-cyclohexyl)-malonic acid di-*tert*-butyl ester 145



2-(3-Oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester **144** (0.312g, 1.0 mmol) in anhydrous methanol (5 mL) was cooled to 0 °C whilst sodium borohydride (0.038 g, 1.0 mmol) was added gradually over 0.1 hours. After 1 hour, the reaction was quenched with distilled water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash-column chromatography (SiO_2, 4:1 petroleum ether/ethyl acetate) gave cis/trans-**145** as a colourless oil (0.311 g, 99%, 80:20 cis/trans). cis/trans-**145**: ^{1}H NMR (400 MHz, $CHCl_3$, 25 °C): δ = 0.90-1.22 (m, 2H), 1.24-1.40 (m, 1H), 1.43 (br s, 18H), 1.50-1.64 (m, 3H), 1.66-1.77 (m, 1H), 1.78-1.83 (m, 1H), 1.93-2.11 (m, 1H), 2.98 (d, J = 9 Hz, 1H, $\mathbf{H}_3$), 2.98 (d, J = 9 Hz, 1H, $\mathbf{H}_3$), 3.59 (m, 1H, $\mathbf{H}_{10ax}$), 4.09 (br s, 1H, $\mathbf{H}_{10eq}$); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 23.6, 27.9 ($\mathbf{C}_6$), 27.9 ($\mathbf{C}_6$), 35.2, 35.9, 39.7, 59.5 ($\mathbf{C}_3$), 70.0 ($\mathbf{C}_{10}$), 81.3 ($\mathbf{C}_5$), 81.3 ($\mathbf{C}_5$), 167.5 ($\mathbf{C}_4$), 167.6 ($\mathbf{C}_4$); IR ($CHCl_3$): ν (cm^{-1}) = 3436 (O-H); 1750 (C=O); MS (FAB+): *m/z* 315 [M^{+}]; CHN analysis: $C_{17}H_{30}O_5$ requires C 64.92%, H 9.62%, found C 64.40%, H 9.62%.

Aluminium isopropoxide transesterification of di-*tert*-butyl malonate 146

Di-*tert*-butyl malonate **146** (0.216 g, 1.0 mmol) and aluminium isopropoxide (0.204 g, 1.0 mmol) were heated to 44 °C in dichloromethane (10 mL). After 24 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give **142** as a yellow oil (< 5% conversion determined by ^{1}H NMR). **142**: ^{1}H NMR (300 MHz, $CHCl_3$, 25 °C): δ = 1.19 (d, J = 6 Hz, 6H, $\mathbf{H}_6$), 3.28 (s, 2H, $\mathbf{H}_1$), 4.99 (sep, J = 2 Hz, 1 H).

Aluminium isopropoxide transesterification of di-*tert*-butyl malonate 146 with 2-cyclohexen-1-ol 112

Di-*tert*-butyl malonate **146** (0.216 g, 1.0 mmol), 2-cyclohexen-1-ol (0.098 g, 1.0 mmol) and aluminium isopropoxide (0.204 g, 1.0 mmol) were heated to 44 °C in dichloromethane (10 mL). After 24 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give **142/148** as a yellow oil (< 5% conversion determined by ^1H NMR).

Attempted preparation of malonic acid dicyclohex-2-enyl ester 148

Dimethyl malonate **114** (0.114 mL, 1.0 mmol), 2-cyclohexen-1-ol **112** (0.2 mL, 2.0 mmol), DPAT (0.032 g, 0.1 mmol) and TMSCl (0.012 mL, 0.1 mmol) were heated to 110 °C in anhydrous toluene (10 mL). After 15 hours, the reaction was cooled, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20:1 petroleum ether/diethyl ether). However a 0% conversion into **148** was obtained (determined by ^1H NMR).

Attempted preparation of malonic acid dicyclohex-2-enyl ester 148

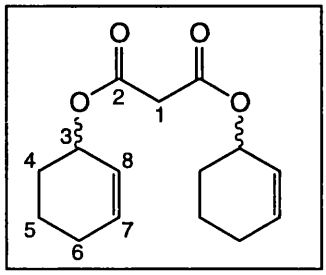
Malonic acid **147** (0.104 g, 1.0 mmol), 2-cyclohexen-1-ol **112** (0.2 mL, 2.0 mmol) and DPAT (0.032 g, 0.1 mmol) were heated to 110 °C in anhydrous toluene (10 mL). After 15 hours, the reaction was cooled, concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 30:1 petroleum ether/diethyl ether). However a 0% conversion into **148** was obtained (determined by ^1H NMR).

Attempted preparation of malonic acid dicyclohex-2-enyl ester 148

Malonic acid **147** (0.104 g, 1.0 mmol), 2-cyclohexen-1-ol **112** (0.2 mL, 2.0 mmol) and cH_2SO_4 (0.2 mL) were heated to 80 °C in anhydrous benzene (10 mL) under Dean-Stark conditions. After 18 hours, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with water (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were

washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **142/148** as a yellow oil (< 5% conversion determined by ^1H NMR).

Preparation of malonic acid dicyclohex-2-enyl ester 148



To a nitrogen-purged flask containing malonic acid **147** (0.104 g, 1.0 mmol), EDC (0.422 g, 2.2 mmol) and DMAP (0.024 g, 0.2 mmol) was added 2-cyclohexen-1-ol **112** (0.2 mL, 2.0 mmol) in dichloromethane (10 mL). After 24 hours at room temperature, the reaction was diluted with dichloromethane (50 mL) and washed with 1 N HCl (50 mL). The aqueous phase was separated and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification by flash-column chromatography (SiO_2, 15:1 petroleum ether/diethyl ether) gave **148** as a colourless oil (0.076 g, 29%). **148**: ^1H NMR (300 MHz, $CHCl_3$, 25 °C): δ = 1.45-1.85 (m, 6H), 1.90-2.05 (m, 4H), 3.28 (s, 4H, $\mathbf{H_1}$), 5.25 (br s, 2H, $\mathbf{H_3}$), 5.55-5.67 (m, 2H, $\mathbf{H_7}$), 5.83-5.95 (m, 2H, $\mathbf{H_8}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.0, 25.2, 28.4, 30.7, 42.6, 66.6 ($\mathbf{C_3}$), 66.6 ($\mathbf{C_3}$), 125.4 ($\mathbf{C_7}$), 125.4 ($\mathbf{C_7}$), 133.5 ($\mathbf{C_8}$), 133.6 ($\mathbf{C_8}$), 166.7 ($\mathbf{C_2}$), 166.7 ($\mathbf{C_2}$); MS (FAB-): *m/z* 315 [M-H$^-$], 183 Da [M-H-$C_6H_8$$^-$].

General procedure for the preparation of 144 in the presence of aluminium isopropoxide

2-Cyclohexen-1-one **113** (0.098 g, 1.0 mmol) and aluminium isopropoxide (0.020 g, 0.1 mmol) in THF (3 mL) were added dropwise to a suspension of sodium hydride (0.002 g, 0.1 mmol) and di-*tert*-butyl malonate **146** (0.216 g, 1 mmol) in THF (7 mL) at 62 °C. After 24 hours under nitrogen, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (50 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **144** as a pale yellow oil (71% conversion determined by ^1H NMR).

General procedure for the aluminium *tert*-butoxide catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol 112 and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester 144

Aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise over a period of 30 minutes to a stirred solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester **144** (0.312 g, 1.0 mmol) in dichloromethane (8 mL) at 44 °C under nitrogen. After 24 hours, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **113/145** as a yellow oil (0.387 g, 94% recovery, > 95% conversion determined by ^1H NMR).

General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one **113** (0.010 g, 0.1 mmol) in dichloromethane (1 mL) were added to a suspension of di-*tert*-butyl malonate **146** (0.624 g, 2.0 mmol) and NaH (0.005 g, 0.2 mmol) in dichloromethane (5 mL) at room temperature. The solution was heated to 44 °C and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise. After 6 hours, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **145/144/113** as a yellow oil (0.673 g, 92% recovery, 19:12:5% conversion determined by ^1H NMR).

General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

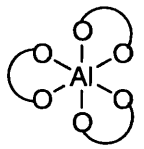
2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester **144** (0.031 g, 0.1 mmol) in THF (2 mL) were added to a suspension of di-*tert*-butyl malonate **146** (0.312 g, 1.0 mmol) and sodium hydride (0.002 g, 0.1 mmol) in THF (6 mL) at room temperature. The solution was heated to 62 °C and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 96 hours, the reaction was cooled, diluted with diethyl ether (50 mL) and

washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **145/144/113** as a yellow oil (0.410 g, 93% recovery, 43:20:5% conversion determined by ^1H NMR).

Procedure for the aluminium acetylacetonate catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol 112 and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester 144

Aluminium acetylacetonate (0.324 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise over a period of 30 minutes to a stirred solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester **144** (0.312 g, 1.0 mmol) in dichloromethane (8 mL) at 44 °C under nitrogen. After 24 hours, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo.* However a 0% conversion into **113/145** was obtained (determined by ^1H NMR).

Attempted preparation of di-*tert*-butyl malonate 146 aluminium acetylacetonate analogue



Di-*tert*-butyl malonate **146** (0.647 g, 3.0 mmol) was added dropwise to $AlCl_3$ (0.133 g, 1.0 mmol) in dichloromethane (5 mL). The reaction was stirred at room temperature for 6 h, then cooled to - 78 °C in a low temperature freezer. After 72 hours, no evidence of a crystalline precipitate was observed.

Attempted preparation of di-*tert*-butyl malonate 146 aluminium acetylacetonate analogue

Di-*tert*-butyl malonate **146** (0.647 g, 3.0 mmol) was added dropwise to $AlMe_3$ (0.25 mL, 2.5 M solution in hexane) in diethyl ether (5 mL). The reaction was stirred at

room temperature for 18 h, then cooled to - 78 °C in a low temperature freezer. After 72 hours, no evidence of a crystalline precipitate was observed.

General procedure for the dimethylaluminium chloride catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol 112 and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester 144

Dimethylaluminium chloride (0.1 mL, 1.0 M solution in hexane, 0.1 mmol) was added to a nitrogen-purged solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) in dichloromethane (3 mL). The reaction was stirred at room temperature for 0.25 h followed by the addition of 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester **144** (0.312 g, 1.0 mmol) in dichloromethane (2 mL). After 24 hours, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **113/145** as a yellow oil (0.369 g, 90% recovery, > 95% conversion determined by ^1H NMR).

General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process

Dimethylaluminium chloride (1.2 mL, 1.0 M solution in hexane, 1.2 mmol) was added to nitrogen-purged solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol), 2-cyclohexen-1-one **113** (0.010 g, 0.1 mmol), di-*tert*-butyl malonate **146** (0.216 g, 1.0 mmol) and sodium hydride (0.002 g, 0.1 mmol) in dichloromethane (3 mL). After 24 hours, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **145/144/113** as a yellow oil (0.309 g, 93% recovery, 25:1:5% conversion determined by ^1H NMR).

General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process

Dimethylaluminium chloride (1.2 mL, 1.0 M solution in hexane, 1.2 mmol) was added to nitrogen-purged (0.25 h) stirred solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) in dichloromethane (2 mL). After 1 h at room temperature, 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester **144** (0.031 g, 0.1 mmol), di-*tert*-butyl malonate **146** (0.216 g, 1.0 mmol) and sodium hydride (0.002 g, 0.1 mmol) in dichloromethane (3 mL) were added. After 90 hours, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **145** as a yellow oil (0.304 g, 91% recovery, 51% conversion determined by ^1H NMR).

5.3 Experimental Procedures: Chapter 3.0 Experimental

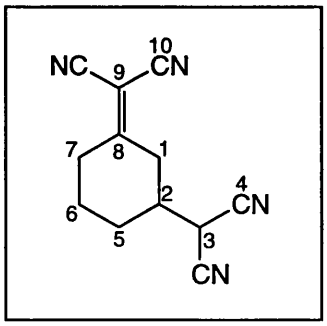
General procedure for the Michael addition screening reactions

2-Cyclohexen-1-one **113** (1.0-5.0 mmol) in solvent (1-5 mL) was added dropwise to suspension of base (0.1-0.5 mmol), where appropriate, and the desired nucleophile (1-5.0 mmol) in solvent (4-10 mL). After 4.5-48 hours at room temperature, the reaction was quenched with acetic acid, washed with water (50 mL) and diluted with diethyl ether (50 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*.

Nucleophile	**Base**	**Solvent [mL]**	***t* [h]**	**Conv. [%][a]**
$NCCH_2CO_2tBu$ (0.734 g)	K*O*tBu (0.058 g)	THF	4.5	91[b]
$NCCH_2CO_2Me$ (0.099 g)	NaH (0.02 g)	THF	24	> 95[5]
$PhCH_2CO_2Me$ (0.495 g)	NaH (0.012 g)	THF	5.5	> 95
CH_3NO_2 (0.061 g)	NaH (0.02 g)	THF	24	< 5
$PhO_2SCH_2SO_2Ph$ (0.709 g)[c]	NaH (0.010 g)	MeOH/CH_2Cl_2	33	0
Meldrum's acid (0.144 g)	K_2CO_3 (0.014 g)	THF	48	Trace[d]
Meldrum's acid (0.144 g)	NaH (0.002 g)	THF	26	0
Meldrum's acid (0.180 g)	NaO*t*Bu (0.010 g)	DMF[e]	24	0
Meldrum's acid (0.180 g)	NaOtBu (0.010 g)	MeCN	24	0
K-Phthalimide (0.185 g)	-	MeOH	24	0
K-Phthalimide (0.185 g)	-	DMF[e]	24	Trace[d]

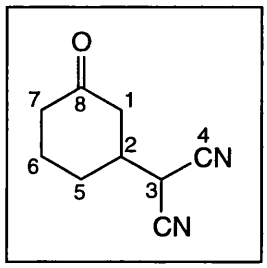
[a] Determined by ^1H NMR. [b] Isolated yield after column chromatography (60:40 petroleum ether/ethyl acetate). [c] Reaction performed at reflux. [d] Detected by MS (CI+). [e] 18-crown-6 (1.25 equiv.) added to improve dissolution.

Preparation of 2-(3-dicyanomethyl-cyclohexylidene)-malononitrile 158



2-Cyclohexen-1-one **113** (0.192 g, 2.0 mmol) in THF (10 mL) was added dropwise to a suspension of sodium *tert*-butoxide (0.019 g, 0.2 mmol) and malononitrile **157** (0.264 g, 4.0 mmol) in THF (10 mL). After 4 hours at room temperature, the reaction was quenched with acetic acid, diluted with dichloromethane (50 mL) and washed with water (100 mL). The aqueous phase was separated and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **158** as a yellow gum (0.306 g, 67%). **158**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.60-1.76 (m, 2H), 2.18-2.46 (m, 5H), 3.12-3.26 (m, 2H), 3.85 (d, J = 5 Hz, 1H, $\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.4, 28.2, 28.8, 30.7, 40.0, 75.3 ($\mathbf{C_3}$), 85.7 ($\mathbf{C_9}$), 111.5 ($\mathbf{C_4}$), 111.5 ($\mathbf{C_{10}}$), 111.6 ($\mathbf{C_4}$), 111.8 ($\mathbf{C_{10}}$), 179.3 ($\mathbf{C_8}$); IR ($CHCl_3$): ν (cm^{-1}) = 2339 (C≡N), 2232 (C≡N), 1598 (C=C); MS (EI+, 70 eV): *m/z* (%) 210 (23) [M^{+}].

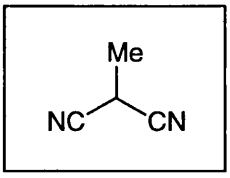
Preparation of 2-(3-oxo-cyclohexyl)-malononitrile 151



2-(3-Oxo-cyclohexyl)-malonic acid dimethyl ester **115** (1.000 g, 4.38 mmol) was stirred for 18 hours in 35% aqueous NH_4OH (5 mL) at room temperature. The aqueous phase was concentrated *in vacuo* to give 2-(3-oxo-cyclohexyl)-malonamide **164** as an off-white solid (0.966 g, 97% recovery). Phosphoryl chloride (0.91 mL, 9.75 mmol) was added to a stirred suspension of 2-(3-oxo-cyclohexyl)-malonamide **164** in anhydrous acetonitrile (25 mL). After 5 hours at 82 °C, the solution was filtered and concentrated *in vacuo*. The oily residue was dissolved in chloroform (100 mL) and extracted with a saturated solution of Na_2CO_3 (2 x 50 mL). The combined

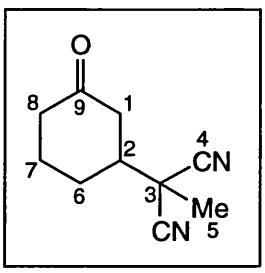
aqueous phases were neutralised with 10% v/v aqueous HCl and NaCl added until a saturated solution was obtained. The aqueous phase was extracted with chloroform (4 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave 2-(3-oxo-cyclohexyl)-malononitrile **151** as a colourless oil (0.593 g, 75%). **151**: ^{1}H NMR (400 MHz, $CHCl_3$, 25 °C): δ = 1.67-1.82 (m, 2H), 2.18-2.27 (m, 2H), 2.29-2.54 (m, 4H), 2.53-2.60 (m, 1H, $\mathbf{H_2}$), 3.75 (d, J = 5 Hz, 1H, $\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.0, 28.4, 39.7, 40.7, 44.6, 75.3 ($\mathbf{C_3}$), 111.5 ($\mathbf{C_4}$), 111.6 ($\mathbf{C_4}$), 206.9 ($\mathbf{C_8}$); MS (EI+, 70 eV): *m/z* (%) 162 (7) [M^{+}]; MS (CI+): *m/z* 163 [MH^{+}].

Preparation of methylmalononitrile 166[6]



In a two-necked flask provided with a reflux condenser, malononitrile **157** (2.64 g, 40.0 mmol), methyl iodide (1.25 mL, 20.0 mmol) and TBAB (0.516 g, 1.6 mmol) were stirred for 0.5 hours at room temperature. Potassium *tert*-butoxide (2.244 g, 20 mmol) was added at 0 °C and the reaction stirred for 0.1 hours. The crude mixture was extracted with dichloromethane (4 x 50 mL). Removal of the solvent *in vacuo* and purification by flash column chromatography (SiO_2, 100% dichloromethane) gave methylmalononitrile **166** as colourless plates (1.124 g, 70%). **166**: ^{1}H NMR (300 MHz, $CHCl_3$, 25 °C): δ = 1.74 (d, J = 7 Hz, 3H), 3.78 (q, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CHCl_3$, 25 °C): δ = 16.3, 75.9, 112.5; IR (KBr): ν (cm^{-1}) = 2659 (C≡N); MS (EI+, 70 eV): *m/z* (%) 79 (58) [M^{+}].

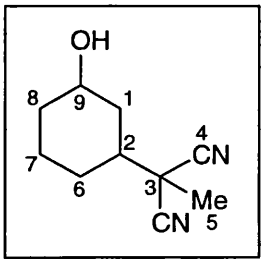
Preparation of 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile 167



2-Cyclohexen-1-one **113** (0.144 g, 1.50 mmol) in THF (3 mL) was added dropwise to a suspension of sodium *tert*-butoxide (0.014 g, 0.15 mmol) and methylmalononitrile **166** (0.120 g, 1.50 mmol) in THF (7 mL). After 4 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and

washed with water (2 x 25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100% diethyl ether) gave **167** as a white solid (0.202 g, 83%). **167**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.63-1.80 (m, 2H), 1.81 (s, 3H), 2.16-2.41 (m, 5H), 2.46-2.54 (m, 1H), 2.67-2.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.5 (**C**$_5$), 23.7, 27.2, 40.5, 42.7, 45.3 (**C**$_3$), 114.5 (**C**$_4$), 115.0 (**C**$_4$), 206.2 (**C**$_9$); IR ($CHCl_3$): ν (cm^{-1}) = 2360 (C≡N), 1700 (C=O); MS (EI+, 70 eV): *m/z* (%) 176 (32) [M^{+}]; HRMS (EI+, 70 eV): $C_{10}H_{12}N_2O$ requires 176.0950, found 176.0952; CHN analysis: $C_{10}H_{12}N_2O$ requires C 68.16%, H 6.86%, N 15.90%, found C 68.10%, H 6.88% N 15.80%.

Preparation of cis/trans-2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile cis/trans-168



2-Methyl-2-(3-oxo-cyclohexyl)-malononitrile **167** (0.016 g, 0.71 mmol) in anhydrous methanol (15 mL) was cooled to 0 °C whilst sodium borohydride (0.027 g, 0.71 mmol) was added portionwise over 0.1 hours. After 1 hour, the reaction was quenched with distilled water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100% diethyl ether) gave cis/trans-**168** as a white solid (0.037 g, 32%, 94:6 cis/trans). cis/trans-**168**: ^{1}H NMR (300 MHz, $CHCl_3$, 25 °C): δ = 1.20 (app dq, *J* = 4, 16 Hz, 2H), 1.41 (app ddt, *J* = 2, 4, 16 Hz, 2H), 1.55-1.80 (m, 3H), 1.71 (s, 3H, **H**$_5$), 1.89-2.10 (m , 2H), 2.22 (app ddt, *J* = 3, 3, 12 Hz, 1H), 3.50-3.65 (m, 1H, **H**$_{9ax}$), 4.23 (br s, 1H, **H**$_{9eq}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, single diastereomer): δ = 22.7 (**C**$_5$), 23.2, 27.5, 35.0, 37.0, 37.4, 43.9 (**C**$_3$), 69.9 (**C**$_9$), 70.0 (**C**$_9$), 115.9 (**C**$_4$), 116.0 (**C**$_4$); IR ($CHCl_3$): ν (cm^{-1}) = 3400 (O-H); MS (CI+): 179 [MH^{+}]; CHN analysis: $C_{10}H_{14}N_2O$ requires C 67.39%, H 7.92%, N 15.72%, found C 66.90%, H 7.84% N 15.50%.

L-Selectride mediated reduction of 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile 167

A solution of 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile **167** (0.088 g, 0.5 mmol) in THF (2 mL) was added dropwise to a nitrogen-purged 1.0 M solution of L-Selectride (0.6 mL, 0.6 mmol) in THF (3 mL) at - 78 °C. After 3 hours, aqueous 3 M NaOH (0.17 mL, 0.5 mmol) was added dropwise followed by slow addition of 30% H_2O_2 (0.55 mL, 12.0 mmol). After a further 0.5 hours stirring at room temperature the mixture was diluted with water (50 mL), extracted with ethyl acetate (5 % 30 mL), washed with brine (100 mL) and the combined organic phases dried (Na_2SO_4). The solvent was removed *in vacuo* to give trans-2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile trans-**168** as a pale yellow solid (0.051 g, 58% recovery). Purification by flash column chromatography (SiO_2, 100% diethyl ether) gave trans-**168** as a white crystalline solid (0.041 g, 47%).

Meerwein-Ponndorf-Verley reduction of 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile 167

2-Methyl-2-(3-oxo-cyclohexyl)-malononitrile **167** (0.176 g, 1.0 mmol) and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) were heated to 82 °C in anhydrous isopropanol (10 mL). After 18 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**168** as a white crystalline solid (0.379 g, 83%).

Meerwein-Ponndorf-Verley equilibration of trans-2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile trans-168

Trans-2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile trans-**168** (0.134 g, 0.75 mmol) and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) were heated to 82 °C in a 1:1 mixture of anhydrous isopropanol/acetone (10 mL). After 12 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography

(SiO_2, 50:50 petroleum ether/diethyl ether) gave cis-**168** (62:38 cis/trans, determined by ^1H NMR) as a white crystalline solid (0.145 g, 100% recovery).

General procedure for the dimethylaluminium chloride catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol 112 and 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile 167

Dimethylaluminium chloride (0.1 mL, 1.0 M solution in hexane, 0.1 mmol) was added to a nitrogen-purged solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) in dichloromethane (3 mL). The reaction was stirred at room temperature for 0.25 h followed by the addition of 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile **167** (0.176 g, 1.0 mmol) in dichloromethane (2 mL). After 15 hours, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **113/168** as a yellow solid (0.294 g, 100% recovery, > 95% conversion determined by ^1H NMR).

General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one **113** (0.009 g, 0.1 mmol) were added to a suspension of methylmalononitrile **166** (0.080 g, 1.0 mmol) and potassium *tert*-butoxide (0.012 g, 0.1 mmol) in dichloromethane (5 mL). The solution was heated to 44 °C under nitrogen and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (3 mL) was added dropwise. After 24 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**168** as a white crystalline solid (0.153 g, 85%).

General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process

Dimethylaluminium chloride (1.0 mL, 1.0 M solution in hexane, 1.0 mmol) was added to nitrogen-purged solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol), 2-cyclohexen-1-one **113** (0.010 g, 0.1 mmol), methylmalononitrile **166** (0.080 g, 1.0 mmol) TBAB (0.012 g, 0.04 mmol) and potassium *tert*-butoxide (0.012 g, 0.1 mmol) in dichloromethane (3 mL). After 24 hours, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 % 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**168** as a white crystalline solid (0.076 g, 45%).

General procedure for the catalytic aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one **113** (0.009 g, 0.1 mmol) were added to a suspension of methylmalononitrile **166** (0.080 g, 1.0 mmol), potassium *tert*-butoxide (0.012 g, 0.1 mmol) and aluminium *tert*-butoxide (0.025 g, 1.0 mmol) in dichloromethane (3 mL). The solution was heated to 100 °C in an ACE pressure tube. After 8 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**168** as a white crystalline solid (0.160 g, 90%).

Procedure for the catalytic cyclohexanone aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and cyclohexanone (0.010 g, 0.1 mmol) were added to a suspension of methylmalononitrile **166** (0.080 g, 1.0 mmol), potassium *tert*-butoxide (0.012 g, 0.1 mmol) and aluminium *tert*-butoxide (0.025 g, 1.0 mmol) in dichloromethane (3 mL). The solution was heated to 100 °C in an ACE pressure tube. After 8 hours, the reaction was cooled, diluted with ether (50 mL) and

washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**168** as a white crystalline solid (0.125 g, 70%).

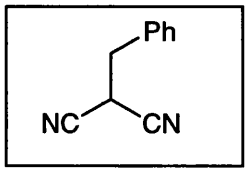
Procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process in toluene

2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one **113** (0.009 g, 0.1 mmol) were added to a suspension of methylmalononitrile **166** (0.080 g, 1.0 mmol) and potassium *tert*-butoxide (0.012 g, 0.1 mmol) in toluene (6 mL). The solution was heated to 110 °C under nitrogen and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (4 mL) was added dropwise. After 24 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**168** as a white crystalline solid (0.034 g, 19%).

General procedure for the potassium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

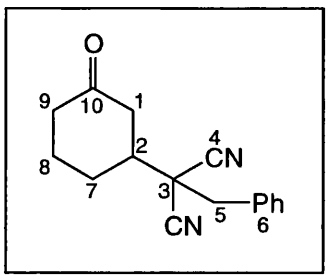
2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one **113** (0.009 g, 0.1 mmol) were added to a suspension of methylmalononitrile **166** (0.080 g, 1.0 mmol) and potassium *tert*-butoxide (0.012 g, 0.1 mmol) in dichloromethane (5 mL). The solution was heated to 44 °C under nitrogen. After 24 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a 0% conversion into cis/trans-**168** (determined by ^1H NMR).

Preparation of benzylmalononitrile 169[6]



In a two-necked flask provided with a reflux condenser, malononitrile **157** (1.32 g, 20.0 mmol), benzyl bromide (1.19 mL, 10.0 mmol) and TBAB (0.257 g, 0.8 mmol) were stirred for 0.5 hours at room temperature. Finely ground potassium carbonate (1.382 g, 10 mmol) was added at 0 °C and the reaction stirred for 6 hours at room temperature. The crude mixture was extracted with dichloromethane (4 x 50 mL). Removal of the solvent *in vacuo* and purification by flash column chromatography (SiO_2, 100% toluene) gave benzylmalononitrile **169** as a white cubic solid (1.091 g, 70%). **169**: m.p 90-92 °C (lit.: 91-92 °C)[7]; ^{1}H NMR (400 MHz, $CHCl_3$, 25 °C): δ = 3.30 (d, *J* = 7 Hz, 2H), 3.91 (t, *J* = 7 Hz, 1H), 7.31-7.44 (m, 5H); IR (KBr): ν (cm^{-1}) = 2256 (C≡N); MS (EI+, 70 eV): *m/z* (%) 156 (13) [M^{+}], 91 (100) ($PhCH_2^{+}$].

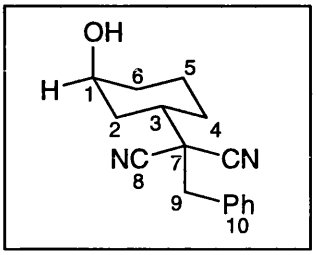
Preparation of 2-benzyl-2-(3-oxo-cyclohexyl)-malononitrile 170



2-Cyclohexen-1-one **113** (0.096 g, 1.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.011 g, 0.1 mmol) and benzylmalononitrile **169** (0.156 g, 1.0 mmol) in THF (3 mL). After 4 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2 x 25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **170** as a cubic white solid (0.217 g, 86%). **170**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.68 (dddd, *J* = 2, 12, 12, 12 Hz, 1H), 1.83 (app dtq, *J* = 1, 4,12 Hz, 1H), 2.22-2.54 (m, 5H), 2.77-2.84 (m, 1H), 3.16 (d, *J* = 14 Hz, 1 H, $\mathbf{H_5}$), 3.15 (d, *J* = 14 Hz, 1 H, $\mathbf{H_5}$), 7.36-7.43 (m, 5H, $\mathbf{H_6}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 23.8, 27.5, 40.6, 43.2, 43.8, 44.7, 44.7, 113.6 ($\mathbf{C_4}$), 114.0 ($\mathbf{C_4}$), 128.9, 128.9, 129.0, 130.0, 130.0, 131.4,

206.2 (**C_{10}**); MS (EI+, 70 eV): *m/z* (%) 252 (37) [M^{+}]; HRMS (EI+, 70 eV): $C_{16}H_{16}N_2O$ requires 252.1263, found 252.1251; CHN analysis: $C_{16}H_{16}N_2O$ requires C 76.16%, H 6.39%, N 11.10%, found C 76.0%, H 6.41% N 11.10%.

Preparation of trans-2-benzyl-2-(3-hydroxy-cyclohexyl)-malononitrile 171



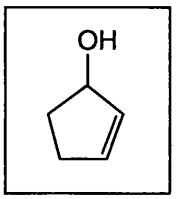
A solution of 2-benzyl-2-(3-oxo-cyclohexyl)-malononitrile **170** (0.590 g, 2.34 mmol) in THF (2 mL) was added dropwise to a nitrogen-purged 1.0 M solution of L-Selectride (2.81 mL, 2.81 mmol) in THF (3 mL) at - 78 °C. After 3 hours, aqueous 3 M NaOH (0.17 mL, 0.5 mmol) was added dropwise followed by slow addition of 30% H_2O_2 (0.55 mL, 12.0 mmol). After a further 0.5 hours stirring at room temperature the mixture was diluted with water (50 mL), extracted with ethyl acetate (5 x 30 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave trans-2-benzyl-2-(3-hydroxy-cyclohexyl)-malononitrile **171** as a white crystalline solid (0.244 g, 41%). trans-**171**: m.p. 106-108 °C; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 0.35 (br s, 1H, O**H**), 0.81 (app. ddt, *J* = 2, 4, 13.5 Hz, 1H, $\mathbf{H}_{6ax}$), 0.96 (app. dq, *J* = 4, 13 Hz, 1H, $\mathbf{H}_{4ax}$), 1.12 (app. dt, *J* = 2, 13 Hz, 1H, $\mathbf{H}_{2ax}$), 1.17-1.21 (m, 1H, H_{5eq}), 1.25 (br d, *J* = 14 Hz, 1H, $\mathbf{H}_{6eq}$), 1.37 (app. tq, *J* = 4, 13 Hz, 1H, $\mathbf{H}_{5ax}$), 1.64 (br d, *J* = 12.5 Hz, 1H, $\mathbf{H}_{4eq}$), 1.70 (br d, *J* = 13 Hz, 1H, $\mathbf{H}_{2eq}$), 1.99 (app. tt, *J* = 3, 12 Hz, 1H, $\mathbf{H}_{3ax}$), 2.41 (d, *J* = 14 Hz, 1H, $\mathbf{H}_7$), 2.51 (d, *J* = 14 Hz, 1H, $\mathbf{H}_7$), 3.53 (br s, 1H, $\mathbf{H}_{1eq}$), 7.02-7.25 (m, 5H, $\mathbf{H}_{10}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.6, 28.7, 32.4, 35.3, 38.7, 40.9, 45.6, 66.0 (**C_1**), 66.1 (**C_1**), 115.0 (**C_8**), 129.1, 129.3, 130.6, 132.8; IR (C_6D_6): ν (cm^{-1}) = 3592 (O-H), 2282 (C≡N); MS (EI+, 70 eV): *m/z* (%) 254 [M^{+}], 91(100) [$PhCH_2^{+}$]; CHN analysis: $C_{16}H_{18}N_2O$ requires C 75.56%, H 7.13%, N 11.01%, found C 74.8%, H 7.34% N 10.30%.

General procedure for the catalytic aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

2-Cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one **113** (0.009 g, 0.1 mmol) were added to a suspension of benzylmalononitrile **169** (0.156 g, 1.0

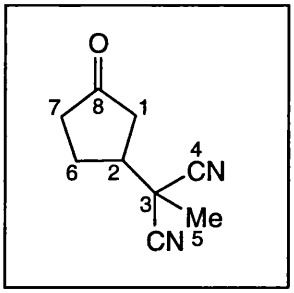
mmol) and potassium *tert*-butoxide (0.011 g, 0.1 mmol) in dichloromethane (3 mL). The solution was heated to 44 °C under nitrogen and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise. After 24 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**171** (0.206 g, 81% yield).

Preparation of 2-cyclopenten-1-ol 173[7]



2-Cyclopenten-1-one **172** (1.000 g, 12.2 mmol) was dissolved in methanol (25 mL) containing $CeCl_3.7H_2O$ (2.273 g, 6.1 mmol) and sodium borohydride (0.461 g, 12.2 mmol) was slowly added with stirring. The mixture was allowed to react for 1 hour at room temperature, followed by hydrolysis (1N aqueous HCl, 30 mL). The mixture was extracted with diethyl ether (2 x 100 mL), washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by distillation under reduced pressure gave **173** as a colourless oil (0.820 g, 80%). **173**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.42 (br s, 1H), 1.64-1.74 (m, 1H), 2.23-2.32 (m, 2H), 2.46-2.55 (m, 1H), 4.87 (br s, 1H), 5.82-5.85 (m, 1H), 5.98-6.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 32.4, 33.7, 77.9, 133.7, 135.4.

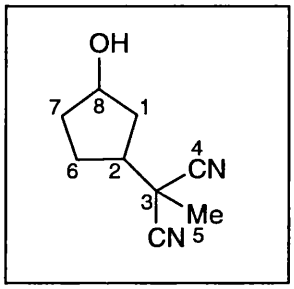
Preparation of 2-methyl-2-(3-oxo-cyclopentyl)-malononitrile 174



2-Cyclopenten-1-one **172** (0.082 g, 1.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.011 g, 0.1 mmol) and methylmalononitrile **166** (0.080 g, 1.0 mmol) in THF (3 mL). After 4 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and

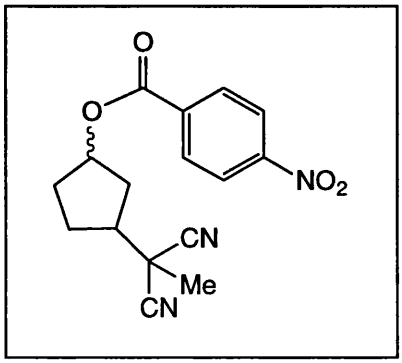
washed with water (2 x 25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **174** as a white solid after recrystallisation from acetonitrile (0.139 g, 86%). **174**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.86 (br s, 3H, $\mathbf{H_5}$), 1.90-2.02 (m, 1H), 2.22-2.39 (m, 2H), 2.41-2.50 (m, 1H), 2.52-2.74 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 23.5 ($\mathbf{C_5}$), 25.8, 35.8 ($\mathbf{C_3}$), 38.2, 40.6, 44.5 ($\mathbf{C_2}$), 114.6 ($\mathbf{C_4}$), 114.7 ($\mathbf{C_4}$), 212.1 ($\mathbf{C_8}$); MS (EI+, 70 eV): *m/z* (%) 162 (21) [M^+]; HRMS (EI+, 70 eV): $C_9H_{10}N_2O$ requires 162.0793, found 162.0795; CHN analysis: $C_9H_{10}N_2O$ requires C 66.65%, H 6.21%, N 17.27%, found C 66.40%, H 6.22% N 17.26%.

Preparation of cis/trans-2-(3-hydroxy-cyclopentyl)-2-methyl-malononitrile 175



2-Methyl-2-(3-oxo-cyclopentyl)-malononitrile **174** (0.415 g, 2.6 mmol) and aluminium *tert*-butoxide (0.640 g, 2.6 mmol) were heated to 82 °C in anhydrous isopropanol (10 mL). After 18 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**175** as a pale yellow oil (0.401 g, 94%, 75:25 cis/trans). cis/trans-**175**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.50-1.70 (m, 1H), 1.72 (br s, 3H, $\mathbf{H_5}$), 1.90-2.20 (m, 3H), 2.25-2.38 (m, 2H), 2.59-2.71 (m, 1H), 4.30-4.34 (m, 1H, $\mathbf{H_{8eq}}$), 4.42-4.45 (m, 1H, $\mathbf{H_{8ax}}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 23.8 ($\mathbf{C_5}$), 24.3 ($\mathbf{C_5}$), 26.9, 26.9, 31.3, 31.3, 34.9, 36.1, 36.3, 39.1, 45.8, 46.3, 72.6 ($\mathbf{C_3}$), 73.1($\mathbf{C_3}$), 115.0 ($\mathbf{C_4}$), 115.1 ($\mathbf{C_4}$), 115.2 ($\mathbf{C_4}$), 116.1 ($\mathbf{C_4}$); IR ($CDCl_3$): ν (cm^{-1}) = 3610 (O-H), 2250 (C≡N); MS (ES+): *m/z* 187 [MNa^+]; CHN analysis: $C_9H_{12}N_2O$ requires C 65.83%, H 7.37%, N 17.06%, found C 63.80%, H 7.55% N 15.60%.

Preparation of cis/trans-4-nitro-benzoic acid 3-(dicyano-methyl-methyl)-cyclopentyl ester cis/trans-177



para-Nitrobenzoyl chloride **176** (0.140 g, 0.85 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of **175** (0.140 g, 0.85 mmol), Et_3N (0.13 mL, 0.94 mmol) and DMAP (0.010 g, 0.09 mmol) in dichloromethane (15 mL). After 4 hours at room temperature, the reaction was quenched with $NaHCO_3$ (30 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-column chromatography (SiO_2, 4:1 petroleum ether/ethyl acetate) gave cis/trans-**177** as a white solid after recrystallisation from ethyl acetate/petroleum ether (0.642 g, 93%, X-ray structure in Appendix 4.6).

General procedure for the aluminium *tert*-butoxide catalysed crossover transfer hydrogenation reaction between 2-cyclopenten-1-ol 173 and 2-methyl-2-(3-oxo-cyclopentyl)-malononitrile 174

Aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise over a period of 30 minutes to a stirred solution of 2-cyclopenten-1-ol **173** (0.084 g, 1.0 mmol) and 2-methyl-2-(3-oxo-cyclopentyl)-malononitrile **174** (0.162 g, 1.0 mmol) in dichloromethane (3 mL) at 44 °C under nitrogen. After 24 hours, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **172/175** as a yellow oil (0.246 g, 100% recovery, 68% conversion determined by ^1H NMR).

General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

2-Cyclopenten-1-ol **173** (0.084 g, 1.0 mmol) and 2-cyclopenten-1-one **172** (0.008 g, 0.1 mmol) were added to a suspension of methylmalononitrile **166** (0.080 g, 1.0 mmol) and potassium *tert*-butoxide (0.011 g, 0.1 mmol) in dichloromethane (3 mL). The solution was heated to 44 °C under nitrogen and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise. After 24 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 % 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**175** (0.044 g, 27% yield).

General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

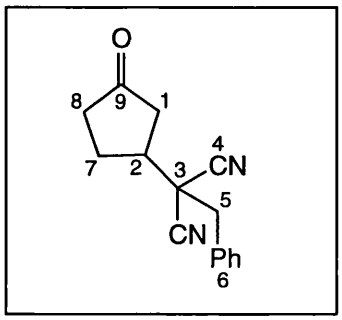
2-Cyclopenten-1-ol **173** (0.084 g, 1.0 mmol) and 2-cyclopenten-1-one **172** (0.008 g, 0.1 mmol) were added to a suspension of methylmalononitrile **166** (0.080 g, 1.0 mmol), potassium *tert*-butoxide (0.011 g, 0.1 mmol) and $CeCl_3.7H_2O$ (0.037 g, 0.1 mmol) in dichloromethane (3 mL). The solution was heated to 44 °C under nitrogen and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise. After 24 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 % 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give cis/trans-**175** (0.172 g, 100% recovery, 10% conversion determined by ^1H NMR).

General procedure for the catalytic aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

2-Cyclopenten-1-ol **173** (0.084 g, 1.0 mmol) and 2-cyclopenten-1-one **172** (0.008 g, 0.1 mmol) were added to a suspension of methylmalononitrile **166** (0.080 g, 1.0 mmol) and caesium fluoride (0.015 g, 0.1 mmol) in dichloromethane (3 mL). Aluminium *tert*-butoxide (0.246 g, 1.0 mmol) was added and the solution heated to 100 °C under nitrogen in an ACE pressure tube. After 20 hours, the reaction was

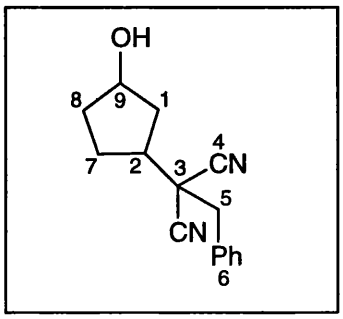
cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 % 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give cis/trans-**175** (0.172 g, 100% recovery, 71% conversion determined by ^1H NMR).

Preparation of 2-benzyl-2-(3-oxo-cyclopentyl)-malononitrile 179



2-Cyclopenten-1-one **172** (0.164 g, 2.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.022 g, 0.1 mmol) and benzylmalononitrile **169** (0.312 g, 2.0 mmol) in THF (3 mL). After 6 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2 x 25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **179** as a cubic white solid (0.280 g, 61%). **179**: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.00-2.14 (m, 1H), 2.25-2.41 (m, 3H), 2.42-2.78 (m, 3H), 3.23 (d, J = 14 Hz, 1H, H_5), 3.24 (d, J = 14 Hz, 1H, H_5), 7.38-7.61 (m, 5H, H_6), MS (EI+, 70 eV): *m/z* (%) 252 (37) [M^{+}]; CHN analysis: $C_{15}H_{14}N_2O$ requires C 75.61%, H 5.92%, N 11.76%, found C 74.80%, H 5.96% N 11.60%.

Preparation of cis/trans-2-benzyl-2-(3-hydroxy-cyclopentyl)-malononitrile 180



2-Benzyl-2-(3-oxo-cyclopentyl)-malononitrile **179** (0.265 g, 1.11 mmol) and aluminium *tert*-butoxide (0.274 g, 1.11 mmol) were heated to 82 °C in anhydrous isopropanol (10 mL). After 13 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**180** as a white crystalline solid (0.214 g, 80%). trans-**180**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.61-1.82 (m, 3H), 1.90-2.10 (m, 2H), 2.13-2.23 (m, 1H), 2.66-2.77 (m, 1H), 3.09 (d, *J* = 14 Hz, 1H, $\mathbf{H_5}$), 3.10 (d, *J* = 14 Hz, 1H, $\mathbf{H_5}$), 4.44 (br s, 1H, $\mathbf{H_9}$), 7.24-7.60 (br s, 5H, $\mathbf{H_6}$); cis-**180**: 4.26-4.35 (m, 1H, $\mathbf{H_9}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, cis/trans-**180**): δ = 27.2, 34.8, 35.2, 38.9, 39.3, 42.5, 42.8, 44.4, 44.6, 44.7, 72.5 ($\mathbf{C_9}$), 72.9 ($\mathbf{C_9}$), 115.3 ($\mathbf{C_4}$), 115.3 ($\mathbf{C_4}$), 129.2, 129.4, 130.5, 132.6, 132.7; MS (ES+): *m/z* 263 [MNa^+]; CHN analysis: $C_{15}H_{16}N_2O$ requires C 74.97%, H 6.71%, N 11.66%, found C 74.70%, H 6.79% N 11.60%.

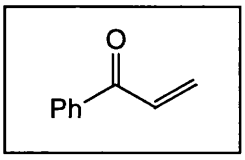
General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

2-Cyclopenten-1-ol **173** (0.084 g, 1.0 mmol) and 2-cyclopenten-1-one **172** (0.008 g, 0.1 mmol) were added to a suspension of benzylmalononitrile **169** (0.156 g, 1.0 mmol) in dichloromethane (3 mL). Aluminium *tert*-butoxide (0.246 g, 1.0 mmol) was added and the solution heated to 100 °C in an ACE pressure tube. After 72 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave cis/trans-**180** as a white crystalline solid (0.144 g, 60%).

General procedure for the control reaction between 2-cyclopenten-1-one 172 and potassium *tert*-butoxide

2-Cyclopenten-1-one **172** (0.082 g, 1.0 mmol) and potassium *tert*-butoxide (0.011 g, 0.1 mmol) were stirred at 44 °C in dichloromethane (5 mL). After 14 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. However, ^1H NMR determined a 0% conversion into condensation-type products.

Preparation of 3-phenyl-1-propen-3-one 183[8]



Manganese dioxide (1.620 g, 18.6 mmol) was added to a suspension of α-vinyl benzyl alcohol **182** (0.500 g, 3.7 mmol) in anhydrous ethyl acetate (40 mL). After 72 hours at room temperature, the solution was filtered through Celite, washed with ethyl acetate (3 % 10 mL) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 petroleum ether/diethyl ether) gave **183** as pale yellow oil (0.177 g, 36%). **183**: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.93 (dd, J = 2, 10 Hz, 1H), 6.43 (dd, J = 2, 17 Hz, 1H), 7.15 (dd, J = 10, 17 Hz, 1H), 7.50-7.82 (m, 5H).

Attempted preparation of 3-phenyl-1-propen-3-one 183

Acryloyl chloride **184** (0.95 mL, 11.6 mmol) was added dropwise to a suspension of aluminium chloride (1.707 g, 12.8 mmol) and anhydrous benzene (1.14 mL, 12.8 mmol) in dichloromethane (10 mL). After 0.3 hours, the reaction was quenched with water (3 mL), diluted with diethyl ether (50 mL) and washed with water (50 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 petroleum ether/diethyl ether) did not afford 3-phenyl-1-propen-3-one **183**.

Attempted preparation of 3-phenyl-1-propen-3-one 183[9]

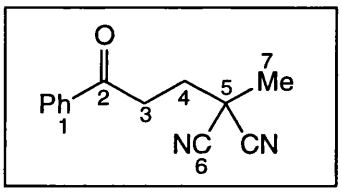
To a stirred solution of α-vinyl benzyl alcohol **182** (0.268 g, 2.0 mmol) in acetone (5 mL), CrO_3 (0.200 g, 2.0 mmol) in water (5 mL) and cH_2SO_4 (0.12 mL, 2.39 mmol) was added at 5 °C. After 3 hours, the reaction was diluted with water (50 mL). The

aqueous phase was separated and extracted with ether (7 % 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 petroleum ether/diethyl ether) gave 3-phenyl-1-propen-3-one **183** as a colourless oil (0.113 g, 43%).

Alternative preparation of 3-phenyl-1-propen-3-one 183[10]

DMSO (0.50 mL, 7.1 mmol) was added dropwise to a cooled (- 78 °C) solution of oxalyl chloride (0.33 mL, 3.75 mmol) in dichloromethane (15 mL). After stirring for 0.1 hours, a solution of α-vinyl benzyl alcohol **182** (0.403 g, 3.0 mmol) was added dropwise *via* a cannula and the reaction mixture stirred at - 78 °C for 1 hour. Et_3N (1.48 mL, 10.7 mmol) was added with the formation of a dense white precipitate. The reaction mixture was warmed to room temperature and poured into water (50 mL). The layers were separated and the aqueous phase extracted with dichloromethane (3 % 30 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 petroleum ether/diethyl ether) gave 3-phenyl-1-propen-3-one **183** as a colourless oil (0.230 g, 60%).

Preparation of 2-methyl-2-(3-oxo-3-phenyl-propyl)-malononitrile 185



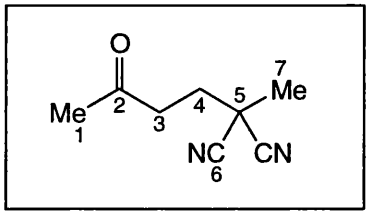
3-phenyl-1-propen-3-one **183** (0.071 g, 0.54 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.006 g, 0.05 mmol) and methylmalononitrile **166** (0.043 g, 0.54 mmol) in THF (3 mL). After 6 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2 x 25 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 petroleum ether/diethyl ether) gave **179** as a white solid (0.071 g, 62%) after recrystallisation from diethyl ether. **179**: ^1H

NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.90 (s, 3H, H_7), 2.42-2.48 (m, 2H, H_4), 3.36-3.42 (m, 2H, H_3), 7.52 (app td, *J* = 1.0, 8 Hz, 2H), 7.63 (app tt, *J* = 2, 7 Hz, 1H), 8.0 (dd, *J* = 1, 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 25.2 (C_7), 33.7, 34.7, 68.3 (C_5), 115.8 (C_6), 128.0, 128.8, 195.9 (C_2); MS (EI+, 70 eV): *m/z* (%) 212 (34) [M^{+}]; CHN analysis: $C_{13}H_{12}N_2O$ requires C 73.57%, H 5.70%, N 13.20%, found C 73.10%, H 5.72% N 13.00%.

Procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process

α-Vinyl benzyl alcohol **182** (0.134 g, 1.0 mmol) and 3-phenyl-1-propen-3-one **183** (0.015 g, 0.1 mmol) were added to a suspension of methylmalononitrile **166** (0.080 g, 1.0 mmol) and potassium *tert*-butoxide (0.011 g, 0.1 mmol) in dichloromethane (3 mL). The solution was heated to 44 °C under nitrogen and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise. After 24 hours, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 % 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (0.209 g, 91%). However a 0% conversion into **186** was obtained (determined by ^1H NMR).

Preparation of 2-methyl-2-(3-oxo-butyl)-malononitrile 189



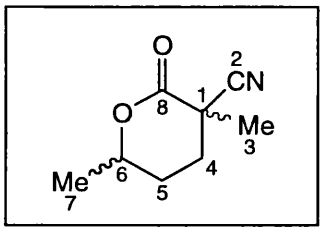
Methyl vinyl ketone **187** (0.070 g, 1.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.011 g, 0.1 mmol) and methylmalononitrile **166** (0.080 g, 1.0 mmol) in THF (3 mL). After 6 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2 x 25 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **189** as a white solid (0.150 g, 73%) after recrystallisation from diethyl ether. **189**: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.84 (s, 3H, H_7), 2.25 (t, *J* = 8 Hz, 2H, H_4), 2.26 (s, 3H,

H_1), 2.86 (t, J = 8 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.2 (C_7), 26.6 (C_1), 33.7, 34.7, 70.3 (C_5), 120.2 (C_6), 195.9 (C_2); MS (EI+, 70 eV): *m/z* (%) 150 (27) [M^{+}].

Procedure for the aluminium *tert*-butoxide catalysed crossover transfer hydrogenation reaction between 3-buten-2-ol 188 and 2-methyl-2-(3-oxo-butyl)-malononitrile 189

Aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise to a stirred solution of 3-buten-2-ol **188** (0.053 g, 0.73 mmol) and 2-methyl-2-(3-oxo-butyl)-malononitrile **189** (0.110 g, 0.73 mmol) in dichloromethane (3 mL) at 44 °C under nitrogen. After 8 hours, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **187/190** as a yellow solid (0.124 g, 76% recovery, 0% conversion determined by ^1H NMR).

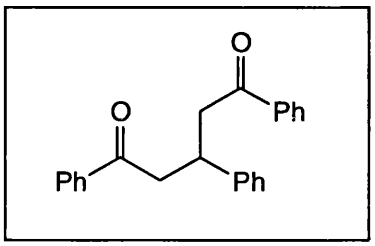
Preparation of 3,6-dimethyl-2-oxo-tetrahydro-pyran-3-carbonitrile 192



2-Methyl-2-(3-oxo-butyl)-malononitrile **189** (0.085 g, 0.57 mmol) in anhydrous methanol (10 mL) was cooled to 0 °C whilst sodium borohydride (0.021 g, 0.57 mmol) was added portionwise over 0.1 hours. After 1 hour, the reaction was quenched with distilled water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **192** as a white diastereomeric (1:1) solid (0.057 g, 66%). **192** (single diastereomer): ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.36 (d, J = 6Hz, 3H, H_7), 1.63 (s, 3H, H_3), 1.92-2.11 (m, 2H, H_5), 2.32-2.43 (m, 1H, H_4), 4.69-4.95 (m, 1H, H_6); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.8 (C_3), 24.5 (C_7), 26.9, 31.8, 37.9, 77.0 (C_6), 120.1 (C_2), 167.3 (C_8); IR ($CDCl_3$): ν (cm^{-1}) = 2250 (C≡N), 1725 (C=O); MS (CI+): *m/z* 154 [MH^{+}]; HRMS (FAB+): $C_8H_{12}NO_2$ requires

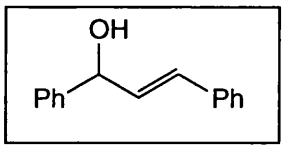
154.0868, found 154.0854; CHN analysis: $C_8H_{12}NO_2$ requires C 62.73%, H 7.24%, N 9.14%, found C 62.10%, H 7.45% N 8.33%.

Isolation of 1,3,5-triphenylpentan-1,5-dione 195[11]



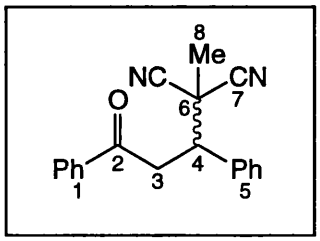
Commercially available chalcone **194** was found to contain a significant impurity, which when isolated by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) was identified as 1,3,5-triphenylpentan-1,5-dione **195**. This impurity could be removed through recrystallisation of chalcone **194** from boiling diethyl ether to give pale yellow needles. **195**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.36 (dd, *J* = 7, 17 Hz, 1H), 3.50 (dd, *J* = 7, 17 Hz, 1H), 4.04-4.09 (m, 1H), 7.16-7.20 (m, 1H), 7.25-7.29 (m, 4H), 7.44 (t, *J* = 8 Hz, 4H), 7.55 (t, *J* = 7 Hz, 2H), 7.95 (d, *J* = 4 Hz, 4H); MS (CI+): *m/z* 329 [MH^+].

Preparation of (*E*)-1,3-diphenyl-prop-2-en-1-ol 193[12]



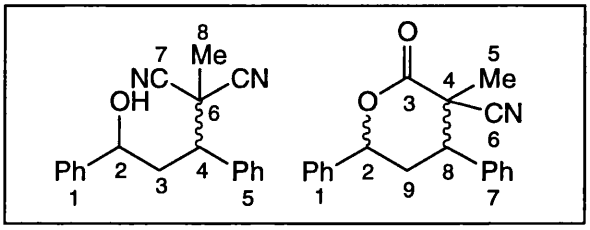
Chalcone **194** (2.080 g, 10.0 mmol) was dissolved in methanol (25 mL) containing $CeCl_3.7H_2O$ (3.720 g, 10.0 mmol) and sodium borohydride (0.378 g, 10.0 mmol) was slowly added with stirring. The mixture was allowed to react for 0.1 hours at room temperature, followed by hydrolysis (1N aqueous HCl, 30 mL). The mixture was extracted with diethyl ether (2 x 100 mL), washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **193** as a colourless solid (1.354 g, 65%) after recrystallisation from petroleum ether. **193**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.32 (br s, 1H), 5.40 (d, *J* = 7 Hz, 1H), 6.41 (dd, *J* = 7, 16 Hz, 1H), 6.72 (d, *J* = 16 Hz, 1H), 7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 75.2, 126.4, 126.7, 127.2, 127.9, 128.7, 128.7, 130.7, 131.7, 136.6, 142.9; IR ($CDCl_3$): ν (cm^{-1}) = 2250 (OH), 1600 (C=C); MS (EI+, 70 eV): *m/z* (%) 210 (24).

Preparation of 2-methyl-2-(3-oxo-1,3-diphenyl-propyl)-malononitrile 196



Chalcone **194** (0.965 g, 1.0 mmol) in THF (7 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.052 g, 0.1 mmol) and methylmalononitrile **166** (0.371 g, 1.0 mmol) in THF (8 mL). After 8 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (100 mL) and washed with water (2 x 50 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8:1 petroleum ether/diethyl ether) gave **196** as a white conformationally restricted solid (1.114 g, 84%) after recrystallisation from diethyl ether. **196**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.59 (s, 3H, $\mathbf{H_8}$), 3.59 (dd, *J* = 2, 16 Hz, 1H, $\mathbf{H_4}$), 3.85 (dd, J = 2, 12 Hz, 1H, $\mathbf{H_3}$), 3.95 (dd, J = 12, 16 Hz, 1H, $\mathbf{H_3}$), 7.19-7.39 (m, 8H), 7.52 (t, *J* = 7 Hz, 1H), 7.88 (d, *J* = 4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.3 ($\mathbf{C_8}$), 37.2, 41.4, 47.8, 116.7 ($\mathbf{C_7}$), 117.0 ($\mathbf{C_7}$), 128.5, 129.2, 129.2, 129.4, 129.5, 134.2, 135.8, 136.4 (not all aromatic signals resolved), 195.5 ($\mathbf{C_2}$); MS (CI+): *m/z* 289 [MH^+]; HRMS (EI+, 70 eV): $C_{19}H_{16}N_2O$ requires 288.1263, found 288.1257; CHN analysis: $C_{19}H_{16}N_2O$ requires C 79.14%, H 5.59%, N 9.72%, found C 78.90%, H 5.62% N 9.69%.

Preparation of 2-(3-hydroxy-1,3-diphenyl-propyl)-2-methyl-malononitrile 197 and 3-methyl-2-oxo-4,6-diphenyl-tetrahydro-pyran-3-carbonitrile 198



2-Methyl-2-(3-oxo-1,3-diphenyl-propyl)-malononitrile **196** (0.100 g, 0.35 mmol) and aluminium *tert*-butoxide (0.085 g, 0.35 mmol) were heated to 82 °C in anhydrous isopropanol (10 mL). After 14 hours under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The

combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 5:1 petroleum ether/diethyl ether) gave **198** and **197** as white crystalline solids (0.068 g, 67%, 67:33 ratio diastereomers, and 0.014 g, 14% respectively, apparent single diastereomer).

197 (single diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.41 (s, 3H, $\mathbf{H_8}$), 2.44-2.55 (m, 1H, $\mathbf{H_3}$), 2.63-2.77 (m, 1H), 4.35 (dd, *J* = 1, 9 Hz, $\mathbf{H_2}$), 4.36 (dd, *J* = 1, 9 Hz, $\mathbf{H_2}$), 7.11-7.39 (m, 10H, $\mathbf{H_{1/5}}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 17.5 ($\mathbf{C_8}$), 25.7, 39.2, 42.2, 51.6, 68.1 ($\mathbf{C_2}$). 74.7 ($\mathbf{C_6}$), 117.4 ($\mathbf{C_7}$), 118.4 ($\mathbf{C_7}$), 128.7, 130.9, 131.2, 131.4, 131.5, 137.0, 144.2 (not all aromatic signals resolved); MS (CI+): *m/z* 291 [MH^+]; HRMS (EI+, 70 eV): $C_{19}H_{18}N_2O$ requires 290.1419, found 290.1419.

198 (single diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.51 (s, 3H, $\mathbf{H_5}$), 2.45 (ddd, *J* = 1, 8, 14 Hz, 1H, $\mathbf{H_9}$), 2.80 (ddd, *J* = 1, 8, 14 Hz, 1H, $\mathbf{H_9}$), 3.02 (dd, *J* = 1, 8 Hz, 1H, $\mathbf{H_8}$), 5.96 (dd, *J* = 1.5, 8 Hz, H_2), 7.26-7.85 (m, 10H, $\mathbf{H_{1/7}}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 169.5 ($\mathbf{C_3}$) (very complicated spectra); MS (CI+): *m/z* 292 [MH^+]; HRMS (EI+, 70 eV): $C_{19}H_{17}NO_2$ requires 291.1259, found 291.1250.

General Procedure for the aluminium *tert*-butoxide catalysed crossover transfer hydrogenation reaction between (*E*)-1,3-diphenyl-prop-2-en-1-ol 193 and 2-methyl-2-(3-oxo-1,3-diphenyl-propyl)-malononitrile 196

Aluminium *tert*-butoxide (0.123 g, 0.5 mmol) in dichloromethane (2 mL) was added dropwise to a stirred solution of (*E*)-1,3-diphenyl-prop-2-en-1-ol **193** (0.104 g, 0.5 mmol) and 2-methyl-2-(3-oxo-1,3-diphenyl-propyl)-malononitrile **196** (0.144 g, 0.5 mmol) in dichloromethane (3 mL) at 44 °C under nitrogen. After 110 hours, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **194/197** as a yellow solid (0.248 g, 100% recovery, 28% conversion determined by ^{1}H NMR).

Procedure for the aluminium *tert*-butoxide catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol 112 and 2-methyl-2-(3-oxo-1,3-diphenyl-propyl)-malononitrile 196

Aluminium *tert*-butoxide (0.123 g, 0.5 mmol) in dichloromethane (2 mL) was added dropwise to a stirred solution of 2-cyclohexen-1-ol **112** (0.049 g, 0.5 mmol) and 2-methyl-2-(3-oxo-1,3-diphenyl-propyl)-malononitrile **196** (0.144 g, 0.5 mmol) in dichloromethane (3 mL) at 44 °C under nitrogen. After 110 hours, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **113/197** as a yellow solid (0.193 g, 100% recovery, 0% conversion determined by ^1H NMR).

5.4 Experimental Procedures: Appendices Experimental

General procedure for the oxidation of 2-cyclohexen-1-ol 112 using rhodium catalysts

Under a nitrogen atmosphere $[Rh(OAc)_2]_2.2H_2O$ (0.096 g, 0.02 mmol) and *ortho*-phenanthroline (0.008 g, 0.08 mmol) were stirred in anhydrous acetone (5 mL) for 0.25 hour. Potassium hydroxide (0.011 g, 0.20 mmol) and 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) in acetone (5 mL) were added dropwise and the suspension was heated to 56 °C. The colour of the reaction mixture changed from blue to a deep purple coloration. After 24 hours the reaction was cooled to room temperature and the catalyst removed by filtration through a pre-packed silica column using ethyl acetate as eluent. The solvent was concentrated *in vacuo* to give 2-cyclohexen-1-one **113** in a 15% conversion (determined by ^1H NMR).

General procedure for ruthenium-catalysed (Bäckvall's catalyst) oxidation of 2-cyclohexen-1-ol 112 by anhydrous acetone

2-Cyclohexen-1-ol **112** (0.098g, 1.0 mmol), $RuCl_2(PPh_3)_3$ (0.096 g, 0.1 mmol) and K_2CO_3 (0.014 g, 0.1 mmol) were weighed into a two-necked round bottom flask equipped with a condenser and a magnetic stirring bar. The reaction system was flushed with nitrogen for 0.25 hour. Anhydrous acetone (5 mL) was added through a syringe and the resulting solution was stirred at 56 °C under nitrogen. After 24 hours the reaction was cooled to room temperature and the catalyst removed by filtration through a pre-packed silica column using ethyl acetate as eluent. The solvent was concentrated *in vacuo* to give 2-cyclohexen-1-one **113** in a 40% conversion (determined by ^1H NMR).

General procedure for ruthenium-catalysed (Bäckvall's catalyst) reduction 2-cyclohexen-1-one 113 by isopropanol

To solid $RuCl_2(PPh_3)_3$ (0.010 g, 0.01 mmol), after evacuation and purging with nitrogen (x 3), was added degassed anhydrous isopropanol (5.0 mL) and the mixture heated at 82 °C for 0.6 hour under nitrogen. 2-Cyclohexen-1-one **113** (0.098 g, 1.0 mmol) in isopropanol (2.5 mL) was added dropwise to the refluxing mixture. The resulting grey suspension was stirred for 10 minutes and then a solution of K_2CO_3 (0.014 g, 0.1 mmol) in isopropanol (2.5 mL) was added dropwise. The resulting

solution rapidly turned to a red homogeneous mixture after the addition of base. After 1 hour the reaction was cooled to room temperature and the catalyst removed by filtration through a pre-packed silica column using ethyl acetate as eluent. The solvent was concentrated *in vacuo* to give 2-cyclohexen-1-o1 **112** in < 5% conversion (determined by ^{1}H NMR).

General procedure for the preparation of 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester 115 using organic bases

2-Cyclohexen-1-one **113** (0.096 g, 1.0 mmol) in THF (3 mL) was added dropwise to a nitrogen-purged THF (5 mL) suspension of phosphazene base **203** (0.003 g, 0.01 mmol) and dimethyl malonate **114** (0.132 g, 1.0 mmol). After 24 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2 x 25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **115** as a pale yellow oil (> 90% conversion determined by ^{1}H NMR).

Preparation of 2-(3-oxo-cyclohexyl)-malonic acid dimethyl ester 115 in cyclohexane

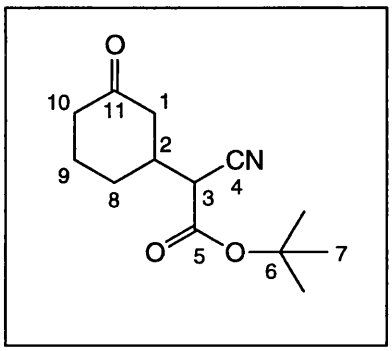
2-Cyclohexen-1-one **113** (0.096 g, 1.0 mmol) in cyclohexane (3 mL) was added dropwise to a nitrogen-purged cyclohexane (5 mL) suspension of phosphazene base **203** (0.003 g, 0.01 mmol) and dimethyl malonate **114** (0.132 g, 1.0 mmol). After 24 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2 x 25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 4:1 petroleum ether/ethyl acetate) gave **144** as a pale yellow oil (0.022 g, 7%).

General procedure for the preparation of 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile 167 using fluoride bases

2-Cyclohexen-1-one **113** (0.096 g, 1.0 mmol) in THF (3 mL) was added dropwise to a THF (5 mL) suspension of caesium fluoride (0.015 g, 0.1 mmol) and methylmalononitrile **166** (0.080 g, 1.0 mmol). After 72 hours at room temperature,

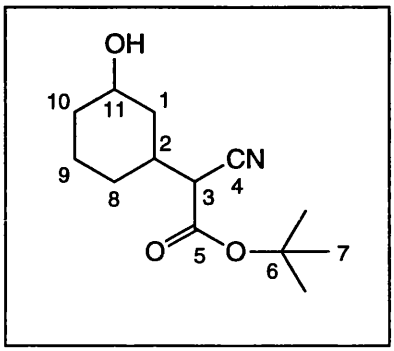
the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2 x 25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **167** as a pale yellow solid (> 90% conversion determined by ^1H NMR).

Preparation of cyano-(3-oxo-cyclohexyl)-acetic acid *tert*-butyl ester 149



2-Cyclohexen-1-one **113** (0.500 g, 5.2 mmol) in THF (5 mL) was added dropwise to a THF (10 mL) suspension of potassium *tert*-butoxide (0.058 g, 0.5 mmol) and *tert*-butylcyanoacetate **202** (0.734 g, 5.2 mmol). After 4.5 hours at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (100 mL) and washed with water (2 x 50 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash-column chromatography (SiO_2, 60:40 petroleum ether/ethyl acetate) gave **149** as a colourless solid (1.043 g, 91%). **149**: ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.51 (br s, 1H, $\mathbf{H_7}$), 1.52 (br s, 1H, $\mathbf{H_7}$), 1.65-1.75 (m, 1H), 1.93-2.00 (m, 2H), 2.14-2.19 (m, 1H), 2.2.7-2.47 (m, 5H), 3.37 (d, J = 5 Hz, 1H, $\mathbf{H_3}$), 3.52 (d, J = 5 Hz, 1H, $\mathbf{H_3}$); MS (CI+): *m/z* 222 [MH^+].

Preparation of cis/trans-cyano-(3-hydroxy-cyclohexyl)-acetic acid *tert*-butyl ester cis/trans-205



Cyano-(3-oxo-cyclohexyl)-acetic acid *tert*-butyl ester **149** (0.221 g, 1.0 mmol) in anhydrous methanol (5 mL) was cooled to 0 °C whilst sodium borohydride (0.038 g, 1.0 mmol) was added portionwise. After 1 hour at 0 °C, the reaction was quenched with distilled water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash-column chromatography (SiO_2, 100%, diethyl ether) gave cis/trans-**205** as a colourless solid (0.144 g, 65%, 90:10 cis/trans). cis/trans-**205**: ^{1}H NMR (400 MHz, $CHCl_3$, 25 °C): δ = 1.13-1.43 (m, 2H), 1.51 (br s, 9H, $\mathbf{H_7}$), 1.51 (br s, 1H, $\mathbf{H_7}$), 1.67-1.71 (m, 1H), 1.72-1.79 (m, 1H), 1.85-1.90 (m, 1H), 1.97-2.15 (m, 3H), 3.33 (d, J = 6 Hz, 1H, $\mathbf{H_3}$), 3.37 (d, J = 6 Hz, 1H, $\mathbf{H_3}$), 3.59-3.69 (m, 1H, $\mathbf{H_{11ax}}$), 4.22 (br s, 1H, $\mathbf{H_{11eq}}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 23.1 ($\mathbf{C_2}$), 23.2 ($\mathbf{C_2}$), 27.8 ($\mathbf{C_7}$), 28.0 ($\mathbf{C_7}$), 29.2, 29.8, 34.8, 34.9, 37.1, 38.2, 39.9, 44.9 ($\mathbf{C_3}$), 45.0 ($\mathbf{C_3}$), 69.8 ($\mathbf{C_{11}}$), 84.2 ($\mathbf{C_6}$), 84.2 ($\mathbf{C_6}$), 115.7 ($\mathbf{C_4}$), 164.5 ($\mathbf{C_5}$), 164.5 ($\mathbf{C_5}$); MS (EI+, 70 eV): *m/z* (%) 206 (100) [$M^{\cdot+}$-H_2O]; MS (CI+): 224 [MH^+].

General procedure for the dimethylaluminium chloride catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol 112 and cyano-(3-oxo-cyclohexyl)-acetic acid *tert*-butyl ester 149

Dimethylaluminium chloride (0.11 mL, 1.0 M solution in hexane, 1.1 mmol) was added to a nitrogen-purged solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol) in dichloromethane (3 mL). The reaction was stirred at room temperature for 0.25 h followed by the addition of cyano-(3-oxo-cyclohexyl)-acetic acid *tert*-butyl ester **149** (0.221 g, 1.0 mmol) in dichloromethane (2 mL). After 6 hours, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were

washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **113**/(±)-**205** as a yellow oil (0.310 g, 97% recovery, 85% conversion determined by ^1H NMR).

General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process

Dimethylaluminium chloride (0.11 mL, 1.0 M solution in hexane, 0.11 mmol) was added to nitrogen-purged solution of 2-cyclohexen-1-ol **112** (0.098 g, 1.0 mmol), 2-cyclohexen-1-one **113** (0.010 g, 0.1 mmol), *tert*-butylcyanoacetate **204** (0.141 g, 1.0 mmol) and sodium *tert*-butoxide (0.020 g, 0.15 mmol) in dichloromethane (3 mL). After 24 hours, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give (±)-**205** as a yellow oil (0.213 g, 85% recovery, < 5% conversion determined by ^1H NMR).

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